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1 | MASH RESOLUTION WITHOUT FIBROSIS WORSENING AFTER BARIATRIC SURGERY IMPROVES LONG-TERM SURVIVAL

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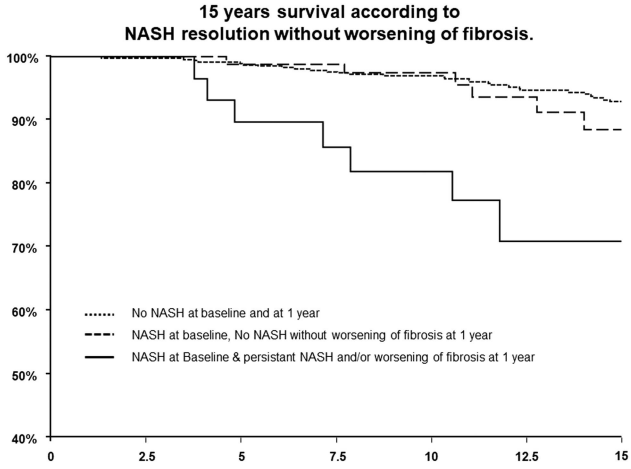
Background: Health agencies are waiting for studies with an extended follow-up evaluating whether *resolution of MASH without worsening of fibrosis* is associated with reduced risk of mortality. This study assessed the impact of histological evolution on long-term survival in MASH patients treated with bariatric surgery. **Methods:** From 1994 to 2022, 2940 bariatric surgery candidates at CHU de Lille were prospectively included. Liver biopsy was performed systematically at baseline and a consecutive biopsy was proposed at one year for MASH patients. We studied in univariate and multivariate analysis the 15-year survival of baseline MASH and fibrosis as well as MASH resolution without worsening of fibrosis after surgery. **Results:** At baseline, liver biopsy was available in 2687 (91%) patients, in whom 232 (8.6%) had biopsy-proven MASH. Paired biopsies before and 1 year after surgery were available in 146/232. Median follow-up of patients with biopsies was 14.7 years. At baseline, MASH patients were different than no-MASH patients for: age 47 vs 42 y, AST 37 vs 22 IU/L, GGT 56 vs 29 IU/L, glucose 133 vs 98 mg/dL, steatosis 60% vs 20% and fibrosis 2 vs 0 ($p < 0.001$ for all), but not for BMI 45.8 vs 46.2 kg/m². At baseline, patients with MASH and patients with significant fibrosis ($\geq$F2) had lower 15-year survival: 83.9% vs 92.7% $p < 0.001$; 79.8% vs 94.0% $p < 0.001$ respectively. After surgery, MASH resolution without worsening of fibrosis was associated with better biological and histological improvement in terms of steatosis 5% (1-20) vs 20% (10-40), fibrosis 1(0-2) vs 3(2-3), AST 21(18-27) vs 29(17-38) IU/L, GGT 22(14-33) vs 32(17-80) IU/L, glucose 93(86-108) vs 104(86-117) mg/dL ($p < 0.001$ for all). MASH resolution was associated with a better 15-year survival in univariate analysis (88.4% vs. 70.8%, $p = 0.009$) and multivariate analysis (HR 0.37, $p = 0.02$) adjusted for age, gender, BMI, diabetes, arterial hypertension, dyslipidemia, and baseline fibrosis. Interestingly, 15-year survival of patients with MASH resolution became similar than those without baseline MASH: 88.4% vs 92.4%, $p = 0.4$ (Figure). 95% of patient with fibrosis regression had MASH resolution. Those achieving a fibrosis regression to F0-F1 at 1 year had a better survival (87.5% vs 69.7% $p < 0.01$); however, it remained lower compared to baseline F0-F1 patients 95.2% vs 87.5% $p = 0.03$. **Conclusion:** Resolution of MASH without worsening of fibrosis is a predictive factor of long-term survival. Fibrosis regression was observed mainly after MASH resolution.



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2 | RIVET TRIAL: PHASE 2 RCT OF RIFAMYCIN SV MMX, A NOVEL RIFAMPIN ANALOGUE, ON GUT-BRAIN AXIS CHANGES IN CIRRHOSIS AND MINIMAL HEPATIC ENCEPHALOPATHY

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Background: Minimal hepatic encephalopathy (MHE) is associated with poor outcomes but treatment strategies are limited. Rifamycin SV MMX (RiVM) is a novel rifampin derivative which a non-absorbable antibiotic with maximal impact in the colon. Aim: Evaluate impact of RiVM on microbiome, safety & gut-brain axis in an RCT. **Methods:** We performed a phase 2 placebo-controlled, double-blind RCT under FDA IND. We randomized cirrhosis outpts with MHE (PHES or Stroop) 1:1 into RiVM or placebo 600 mg BID (1200 mg) BID for 30 days with 7 day post-drug f/u. There were 4 visits; baseline, day 7, 15 & 30. *Primary outcome* was stool microbial change (cirrhosis dysbiosis ratio CDR, high = good) in rifamycin vs placebo through 16SrRNA sequencing from baseline to day 30 (end). CDR is the ratio of *Lachnospiraceae* + *Ruminococcaceae* + *Veillonellaceae* to *Enterobacteriaceae* + *Bacteroidaceae*. Secondary outcomes were gut-brain (cognition, serum ammonia, optional brain MR spectroscopy, MRS), inflammatory (stool calprotectin), PROs (SIP: total, physical, psychosocial, high = worse) and handgrip strength. Comparisons between/within gps & delta (Δ Post minus Pre) values were compared. **Results:** 58 pts were screened; 8 had overt HE, 11 screen failed due to no MHE on testing, 9 were not interested. Ultimately 30 pts were enrolled (15/gp), who completed the study without any safety concerns, including the post-drug visit with good adherence. Groups were largely equivalent on baseline but ammonia & SIP scores were higher in RiVM vs placebo (Fig B). 7 RiVM and 11 placebo-assigned pts agreed & were eligible for the optional brain MRS. Microbiota: CDR decreased in RiVM pts due to ↓*Lachnospiraceae* & *Ruminococcaceae*, although *Bacteroidaceae*↑. There was ↓α-diversity & significant β-diversity change with clustering of post-RiVM vs pre & post-RiVM vs post-placebo (Fig D/E). Labs: No change in MELD-Na but ammonia & calprotectin decreased in RiVM vs baseline and Δ ammonia was higher in RiVM (Fig B); no change in placebo. Cognition and Brain MRS: Although serial dotting, which tests for psychomotor speed improved in RiVM, no other changes were seen within/between gps. Brain Glutathione ↑with RiVM & decreased in placebo ($p = 0.03$) on brain MRS but remaining metabolites (choline, myoinositol, glutamate/glutamine) remained similar. PROs: ΔPhysical SIP and handgrip were higher indicating improved strength & better physical QOL with RiVM vs placebo. **Conclusion**: In this phase 2 double-blind, placebo-controlled RCT of rifamycin SVMMX in patients with cirrhosis and MHE, we found no safety concerns. RiVM Rx resulted in lowered gut microbial α-diversity and cirrhosis dysbiosis ratio. RiVM therapy was associated with reduction in blood ammonia and improved physical function and handgrip. There was also a reduction in brain oxidative stress with RiVM but no change in cognitive testing. RiVM, with predominant colonic action, may have important gut-brain axis modulatory impact in cirrhosis and MHE.

Fig A	Rifamycin SV MMX (n=15)		Placebo (n=15)	
	Baseline	Drug-end	Baseline	Drug-end
Microbiota				
Shannon diversity	**2.45±0.34**	**2.12±0.33*‡**	2.46±0.54	2.47±0.41
CDR	**1.43±1.29**	**1.11±2.35***	1.71±1.9	2.8±4.06
Labs				
MELD-Na	9.0±3.0	8.7±2.7	7.7±2.0	8.4±3.1
Ammonia	**52.1±31.9†**	**39.9±20.1*‡**	26.5±10.4	26.8±10.3‡
Calprotectin	346±766	82.6±57.3*	116.2±124.2	97.5±93.4
Cognition				
PHES (high=good)	-5.3±2.3	-5.0±2.9	-4.0±2.9	-3.6±3.3
NCTA	55.8±26.4	52.2±24.9	48.0±17.2	45.5±15.3
NCTB	137.3±55.5	157.1±77.6	127.5±60.2	124.9±51.9
DST	37.9±6.6	37.2±7.6	46.6±11.6	47.4±11.0
SDT	80.7±15.5	72.4±16.5*	73.7±16.6	70.9±18.4
LTTerrors	43.0±22.9	48.6±27.9	32.5±12.0	33.6±14.7
LTTtime	82.1±25.8	83.0±32.1	81.3±18.7	73.1±25.3
Stroop (low=good)				
Total time	218.5±47.2	229.3±49.9	196.9±34.7	198.8±42.9
OffTime	99.4±21.5	103.4±29.0	90.1±15.3	91.7±21.4
OnTime	119.1±29.4	121.7±29.9	106.8±21.2	108.1±23.8
PROs				
SIP total	18.4±13.3	15.5±10.4	12.2±10.5	12.8±11.3
SIP physical	16.8±10.2†	13.2±10.1*‡	8.7±10.3	10.3±11.2
SIP psychol	18.9±18.2	15.6±14.6	13.6±13.0	14.4±14.7
Grip Strength	26.7±9.3	28.0±11.1	33.4±12.8	31.1±11.5

*: p<0.05 within groups, †p<0.05 between groups baseline ‡p<0.05 between groups end of study

Fig B: Delta (End minus Baseline)	Rifamycin SV MMX (n=15)	Placebo (n=15)	P value	Interpretation
Labs				
MELD-Na	-0.07±1.53	0.71±1.90	0.21	No change
Ammonia	**-11.4±19.8**	**0.24±8.56**	**0.05**	**Ammonia ↓ w RiVM**
Calprotectin	-263±777	-14.4±61.6	0.24	No change
Cognition & PROs				
PHES	0.33±1.99	0.53±1.50	0.62	No change
Stroop total	12.8±29.1	1.9±18.6	0.11	No change
SIP total	-2.87±6.50	0.65±5.86	0.12	No change
SIP physical	**-2.76±5.44**	**1.62±5.76**	**0.03**	**QOL↑ RiVM**
SIP psycho	-3.34±9.26	0.9±12.4	0.28	No change
Handgrip	**1.34±4.53**	**-2.29±5.24**	**0.04**	**Grip↑ RiVM**
Microbiota				
CDR	-0.31±2.46	1.09±3.24	0.18	No change
Shannon diversity	-0.29±0.497	0.004±0.53	0.12	No change

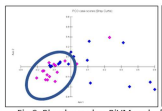

Fig C: Placebo end vs RiVM end purple points in the blue oval show separate clustering

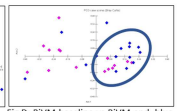

Fig D: RiVM baseline vs RiVM end, blue points in the blue oval show separate clustering

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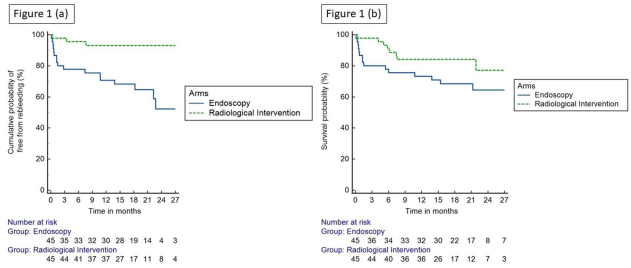
3 | SERIAL ENDOSCOPIC INJECTION SCLEROTHERAPY WITH N BUTYL CYANOACRYLATE GLUE VERSUS RADIOLOGICAL INTERVENTION FOR SECONDARY PROPHYLAXIS OF GASTRIC VARICEAL HEMORRHAGE IN PATIENTS WITH LIVER CIRRHOSIS (CRISP-GV): A RANDOMIZED CONTROLLED TRIAL★

Sagnik Biswas, Manas Vaishnav, Shekhar Swaroop, Umang Arora, Arnav Aggarwal, Piyush Pathak, Abhinav Anand, Anshuman Elhence, Deepak Gunjan, Saurabh Kedia, Soumya Jagannath Mahapatra, Shivanand Gamanagatti and Dr Shalimar, All India Institute of Medical Sciences, New Delhi

Background: Acute variceal bleed (AVB) from cardiofundal varices (GOV-2/IGV-1) is associated with high mortality rates in patients with liver cirrhosis. No consensus exists on the best modality to prevent rebleeding after an index episode of bleeding. **Methods:** Consecutive cirrhosis patients with AVB from cardiofundal varices, after primary hemostasis by endoscopic obturation with cyanoacrylate glue (CYA), were randomized into two arms. In the 'endoscopic intervention' (EI) arm, endoscopic obturation with CYA was repeated at regular intervals (1, 3, 6 and 12 mo); while in the 'radiological intervention' (RI) arm, patients underwent transjugular intrahepatic portosystemic shunt (TIPS) or balloon-occluded retrograde transvenous obliteration (BRTO); preferably BRTO, if a shunt vessel was present. Hepatic venous pressure gradient (HVPG) was measured at baseline and 1 month. Primary outcome measures included rebleed rates and all-cause mortality at 1 year. **Results:** We randomized 90 patients (n = 45 in each arm), median age 46 (35-55) years with mean (±SD) Child and MELD scores at baseline 7.4 ± 1.8 and 12.3 ± 3.2, respectively. Alcohol was the predominant etiology of cirrhosis in 33 (36.7%) patients. There were no differences in baseline characteristics between the two arms. In the RI arm, 25 patients underwent BRTO and 20 underwent TIPS. Median follow-up was 17.9 and 16.4 months, for EI and RI arms, respectively. Rebleed rates at 1 year were significantly higher in the EI arm compared to RI arm: 13 (28.9%) vs 3 (6.7%); $p = 0.010$ (Figure 1a). Mortality at 1 year was 12 (26.7%) in the EI arm versus 7 (15.6%) in the RI arm ($p = 0.108$) (Figure 1b). Technical success for glue injection, TIPS and BRTO was 100%, 100% and 96.2% respectively. Worsening of ascites after radiological intervention was reported by 12 (26.7%) patients versus 2 (4.4%) in EI arm; $p = 0.007$. On sub-group analysis, patients undergoing BRTO had a statistically insignificant median rise in HVPG (2 mm versus 1 mm of Hg; $p = 0.715$) and aggravation of esophageal varices on follow-up (24% versus 11%; $p = 0.150$) compared to the EI arm. There was no significant difference in complications, rebleeding rates and overall mortality at 1 year between those undergoing TIPS as compared to BRTO. The probability of remaining free from all-cause rebleeding at 1 and 2 years was 70.7% versus 93%, and 52.3% versus 93% for the EI and RI arms, respectively (Figure 1a). **Conclusion:** Radiological intervention for secondary prophylaxis significantly reduces rebleeding in patients with liver cirrhosis with GV hemorrhage but does not provide any survival benefit. TIPS and BRTO have comparable complications, rebleeding and mortality rates on follow-up.

Figure 1
(a) Kaplan Meier curve demonstrating cumulative freedom from rebleeding between the endoscopy and radiological intervention arm at 1 year (Log-rank p<0.001)
(b) Kaplan Meier curve demonstrating differences in overall survival between the endoscopy and radiological intervention arm at 1 year (Log-rank p=0.108)



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4 | FIBROSIS IMPROVEMENT WITH PEGOZAFERMIN TREATMENT IN MASH PATIENTS WITH F4 FIBROSIS: ANALYSIS FROM A 24-WEEK RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2 TRIAL (ENLIVEN)

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

Ocala GI Research, (11)89bio, CA, (12)Mayo Clinic, Rochester, MN

Background: Metabolic dysfunction-associated steatohepatitis (MASH) patients who have developed stage F4 fibrosis (cirrhosis) are at risk of hepatic decompensation, hepatocellular carcinoma, liver transplant, cardiovascular events, liver and all-cause mortality. There are currently no approved therapies for non-cirrhotic or cirrhotic MASH. **Methods:** The ENLIVEN Phase 2b study assessed the effect of treatment for 24 weeks with one of three doses of pegozafermin or placebo on liver histology endpoints in 222 subjects with biopsy confirmed MASH (fibrosis F2 or F3, NAS ≥ 4 points). Initially, biopsies were assessed by one of two central pathologists; during the study, a novel 3-panel consensus scoring method was introduced to increase objectivity in biopsy reading. Baseline biopsies of subjects enrolled prior to this change were re-read by the panel. Fourteen subjects who met the study histological inclusion criteria based on the original read were re-classified as having stage F4 fibrosis by the consensus panel. All subjects had well compensated cirrhosis. We present post-hoc descriptive data for these subjects. **Results:** Baseline characteristics included: female 57%, mean age 56, average BMI 36.8, mean MRI-PDFF 15%, mean ProC3 65ng/mL, and 86% with a history of diabetes. Treatment assignment of the 14 subjects was: Placebo n = 2; Pooled pegozafermin (PGZ) n = 12. Follow-up biopsies at week 24 were available for 12 of the 14 subjects (PBO n = 1; PGZ pooled n = 11). PGZ led to $\geq$ 1 stage fibrosis improvement in 9 of the 11 treated patients (82%), and to $\geq$ 1 stage fibrosis improvement without worsening of MASH in 5/11 (45%) subjects. No fibrosis improvement was observed in the placebo group. There was concurrent improvement compared to baseline in the non-invasive fibrosis biomarkers ProC3 and FAST (LS means difference -24% and -53%, respectively). Treatment with PGZ also reduced ALT at week 24 compared to baseline (LS mean -53%). Pegozafermin was well tolerated in these subjects with the most common treatment-emergent adverse events being GI side effects and injection site reactions. No severe adverse events, discontinuations, or deaths were reported. **Conclusion:** These data demonstrate robust fibrosis improvement at 24 weeks in patients with MASH-related cirrhosis who were treated with PGZ. In addition to regression of fibrosis, reductions were observed in liver specific biomarkers of fibrogenesis/fibrosis (ProC3 and FAST) and inflammation (ALT). Pegozafermin appears to maintain a safety and tolerability profile in patients with compensated cirrhosis comparable to those with less advanced disease (MASH with F2/F3 fibrosis). Although this small subset precludes statistical analysis, the numerical improvement observed across both histology and biomarkers is encouraging and supports further evaluation of PGZ as a treatment for subjects with compensated MASH cirrhosis.

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♦ 5 | ANALYZING NEW ONSET HEPATIC DECOMPENSATION AND LONG TERM ABSTINENCE/CRAVING IN PATIENTS WITH ALCOHOL ASSOCIATED LIVER DISEASES (AALD): A DOUBLE BLIND RANDOMIZED CONTROL TRIAL (RCT) FOR EFFECTIVENESS OF SELF ADMINISTERED 12 WEEKS 50 MG ORAL NALTREXONE VERSUS PLACEBO; ALONG WITH STANDARD COUNSELLING★

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8 | POSITIVE RESULTS FROM THE ALPINE 4 STUDY: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, PHASE 2b TRIAL EVALUATING MULTIPLE DOSES OF THE FGF19 ANALOGUE ALDAFERMIN IN PATIENTS WITH COMPENSATED CIRRHOSIS DUE TO NONALCOHOLIC STEATOHEPATITIS

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Background: Patients with cirrhosis are at increased risk of liver decompensation and HCC which can result in liver transplant or death. There is no available therapy and previous clinical trials have failed to show a benefit in patients with NASH and cirrhosis. Aldafermin, an engineered analog of the human hormone FGF19, improved liver histology in previous non-cirrhotic, phase 2 trials. We report results from ALPINE 4, a 48-week, phase 2b paired liver biopsy study in patients with compensated cirrhosis due to NASH (NCT04210245). **Methods:** 160 patients were randomized to receive placebo (PBO, n = 56), aldafermin 0.3mg (n = 7; enrollment in the 0.3mg arm was discontinued during trial to allow patients exposure to higher doses), 1mg (n = 42), or 3 mg (n = 55) SC QD at 48 sites in 8 countries. Key inclusion criteria included compensated cirrhosis (CTP-A) with biopsy-proven NASH (NASH CRN criteria). Patients underwent liver biopsy at baseline and week 48. The primary endpoint was the change in Enhanced Liver Fibrosis (ELF) score from baseline to week 48 vs. PBO. Secondary endpoints included fibrosis improvement of ≥ 1-stage, C4, serum bile acids, Pro-C3, ALT and AST. Primary analysis was performed in the ITT population using MMRM method. **Results:** Demographic and baseline characteristics were similar across the trial groups. The mean age was 59.6 (8.2) years and 76% of patients had T2D at baseline. The primary endpoint was achieved with aldafermin 3mg. At week 48, the least-squares (LS) mean difference between aldafermin and PBO in ELF was −0.1 for 1mg and −0.5 for 3mg ($p < 0.001$) (Table 1). Fibrosis improvement of ≥ 1-stage was achieved in 15%, 21% and 23% patients in the PBO, 1mg and 3mg groups, respectively. Dose-dependent reductions in C4 (LS mean difference vs. PBO: −65% and −72% in 1mg and 3 mg groups), total bile acids (−67%, −82%), the fibrogenesis biomarker Pro-C3 (−54%, −60%), ALT (−30%, −35%), and AST (−19%, −28%) were observed. Adverse events were mostly mild and moderate in severity. Six (6%) patients on aldafermin discontinued treatment due to drug-related adverse events. Serious adverse events occurred in 19 (12%) patients, all deemed unrelated to drug. No DILI or HCC was reported in the study. **Conclusion:** We herein report positive primary endpoint results in a randomized controlled trial of aldafermin in patients with NASH and compensated cirrhosis. Aldafermin achieved dose-dependent benefits in ELF and other non-invasive markers of both inflammation and fibrosis.

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Table 1. Change from baseline to week 48 in key endpoints.

	PBO (n=56)	Aldafermin 1mg (n=42)	Aldafermin 3mg (n=55)
Primary Endpoint			
ELF (baseline)	10.6 (1.0)	10.6 (0.8)	10.6 (1.1)
Δ ELF		−0.1 *P=0.31 vs. PBO*	−0.5 *P<0.001 vs. PBO*
Secondary Endpoints			
% Patients achieving fibrosis improvement of ≥1-stage	15%	21% *P=0.39 vs. PBO*	23% *P=0.36 vs. PBO*
C4 (baseline), ng/mL	45.4 (33.5)	38.7 (25.7)	43.7 (37.9)
Δ C4, ng/mL		−23.6 *P<0.001 vs. PBO*	−27.5 *P<0.001 vs. PBO*
Δ C4, Relative, %		−65.1 *P<0.001 vs. PBO*	−71.8 *P<0.001 vs. PBO*
TBA (baseline), umol/L	10.3 (10.0)	9.2 (8.2)	12.7 (14.1)
Δ TBA, umol/L		−5.6 *P=0.022 vs. PBO*	−6.3 *P=0.005 vs. PBO*
Δ TBA, Relative, %		−67.3 *P<0.001 vs. PBO*	−82.3 *P<0.001 vs. PBO*
Pro-C3 (baseline), ng/mL	47.1 (28.3)	48.7 (27.5)	59.2 (54.9)
Δ Pro-C3, ng/mL		−22.1 *P=0.017 vs. PBO*	−25.9 *P=0.003 vs. PBO*
Δ Pro-C3, Relative, %		−54.0 *P=0.07 vs. PBO*	−60.0 *P=0.032 vs. PBO*
ALT (baseline), U/L	45.6 (31.2)	46.4 (23.2)	51.2 (29.6)
Δ ALT, U/L		−13.5 *P<0.001 vs. PBO*	−17.0 *P<0.001 vs. PBO*
Δ ALT, Relative, %		−29.6 *P<0.001 vs. PBO*	−35.2 *P<0.001 vs. PBO*
AST (baseline), U/L	36.9 (21.1)	39.5 (19.4)	45.0 (25.7)
Δ AST, U/L		−7.3 *P=0.018 vs. PBO*	−11.6 *P<0.001 vs. PBO*
Δ AST, Relative, %		−18.8 *P=0.004 vs. PBO*	−27.9 *P<0.001 vs. PBO*
LSM (baseline), kPa	22.9 (12.1)	23.3 (10.8)	22.7 (13.8)
Δ LSM, kPa		−4.1 *P=0.08 vs. PBO*	−2.3 *P=0.32 vs. PBO*
Δ LSM, Relative, %		−30.1 *P=0.036 vs. PBO*	−21.3 *P=0.12 vs. PBO*

Baseline values are mean (SD); least-squares means difference *vs.* placebo (PBO) or percentage of patients are shown. Enrollment in the 0.3mg dose group was discontinued early during trial to allow patients exposure to higher doses, thus not included in the analysis due to small N numbers.

Primary analysis was performed in the intention-to-treat (ITT) population using mixed-model repeated measures (MMRM) method. Fibrosis improvement was analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by baseline T2D status and randomization ratio.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; C4, 7alpha-hydroxy-4-cholesten-3-one; ELF, enhanced liver fibrosis; LSM, liver stiffness measure by Fibroscan; Pro-C3, neoepitope-specific N-terminal propeptide of type III collagen; TBA, serum total bile acids.

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9 | VALIDATION OF THE R3-AFP MODEL FOR RISK PREDICTION OF HCC RECURRENCE AFTER LIVER TRANSPLANTATION IN THE SILVER CLINICAL TRIAL

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Background: Hepatocellular carcinoma (HCC) recurrence risk after liver transplantation (LT) has been evaluated with different prediction models following pathology explant analysis. The inclusion of alpha-feto protein (AFP) in these models, such as the novel R3-AFP score (1), have significantly improved risk stratification of HCC recurrence post-LT. The SiLVER trial (NCT00355862) evaluated the efficacy of mTOR inhibitors (Sirolimus-Group B) compared to mTOR-free based immunosuppression (Group A) to reduce post-LT HCC recurrence (2). Here, we aimed to validate the prognostic and predictive discrimination power of R3-AFP scoring on the intention-to-treat population (ITT) included in the SiLVER trial (NCT00355862). **Methods:** We included the intention-to-treat (ITT) patient population from the SiLVER Study. Cox proportional hazard survival analysis was performed, estimating hazard ratios (HR) and 95% confidence intervals (95% CI). Discriminant function was evaluated using the Harrell's c-index. A competing risk regression analysis was also conducted estimating sub-HR. Calibration was conducted through expected versus observed events estimating the baseline hazard. **Results:** Overall, 528 patients signed written informed consent of which 20 were excluded for the intention-to-treat analysis (Group A, n = 256 ; Group B, n = 252). The 5-year recurrence rate in the ITT population was 18.7% (95% CI

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intensity of > 1,000 in both MSC-EVs of healthy individual's and that of patients with DLC in our clinical trial. Among these miRNAs, ten miRNAs highly expressed in MSC-EVs and lowly expressed in HHSteCs. Each miRNA mimic of the ten miRNAs was transfected into activated HHSteCs and we identified five miRNAs which suppress expression of any of ECM genes ($p < 0.05$). Furthermore, transfection of a combination of the five miRNAs into activated HHSteC resulted in a significant decrease in expression of COL1A1, COL1A2, COL3A1, and ELN ($p < 0.05$). **Conclusion:** This study identified five anti-fibrotic miRNAs enriched in MSC-EVs and provided insight into mechanisms of action of MSC-EVs in fibrosis regression. Hence, miRNAs in MSC-EVs may be potential biomarkers for functional assessment of MSCs in liver regeneration therapy.

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28 | MACROPHAGE HETEROGENEITY DURING MASH REGRESSION UNVEILS MULTIFACETED TREM2 DEPENDENT MECHANISMS THAT FACILITATE MASH AND FIBROSIS RESOLUTION

Souradipta Ganguly[1], Kei Ishizuka[1], Brin Rosenthal[1], Nathalia Castorena[1], Aryaman Bhattacharya[1], Tatiana Kisseleva[1], David A. Brenner[1,2] and Debanjan Dhar[1], (1)University of California, San Diego School of Medicine, (2)Sanford Burnham Prebys Medical Discovery Institute

Background: Macrophage (MF) are recruited to the liver during MASH progression, including fibrogenic TREM2+ hepatic lipid associated MF (LAMs). However, the TREM2 receptor itself is anti-fibrotic, in that *Trem2*$^{-/-}$ mice have more severe MASH than WT mice. Despite these recent studies, little is known about mechanisms that regulate MF function during MASH regression. We studied Trem2 expression in MF across the MF clusters during MASH regression, identified MF sub-populations that aid in MASH resolution, and investigated whether Trem2 is required for efficient MASH regression and the underlying mechanisms. **Methods:** Foz (*Alms1*$^{-/-}$)[1] and Foz::*Trem2*$^{-/-}$ mice on Western Diet (WD) developed MASH by 12w[1]. Foz mice are hyperphagic and develop MASH on a WD. Regression was studied by switching MASH mice to normal chow for an additional 4-8w. scRNAseq elucidated MF gene signatures and pathways. In vitro experiments were performed with bone marrow derived MF (BMDM) from WT and *Trem2*$^{-/-}$ mice. **Results:** Absence of Trem2 impaired fibrosis, inflammation and steatosis resolution during MASH regression. scRNAseq revealed two Trem2-expressing MF sub-populations during MASH progression and regression in Foz+WD mice: (i) Monocyte derived MF that occupy the Kupffer cell niche (MoKC), and (ii) hepatic lipid associated MF (LAM). While MoKC was the major MF sub-population during MASH progression, it decreased during regression with reduced Trem2 expression. LAMs maintained Trem2 expression and expanded, becoming the dominant MF sub-population during regression. Within the regression livers, scRNA-seq revealed that Trem2-hi MF were highly enriched in MASH-resolving pathways (extracellular matrix degradation, phagocytosis and lipid handling). Trem2-low MF, on the other hand, expressed disease worsening pathways (inflammation, cell death). While hepatic LAMs have mostly been studied in the context of MASH progression, our findings demonstrate that during regression they resemble restorative MF, with increased expression of MMPs and phagocytosis-related genes. *In vitro* experiments demonstrated superior collagen degradation ability by Trem2+ BMDMs compared to their Trem2- counterparts. **Conclusion:** This study expands our understanding of MF heterogeneity in MASH by uncovering distinct sub-populations during regression. We highlight the significance of Trem2 in mediating MASH regression and delve into the multiple probable mechanisms through which Trem2 achieves this effect. Animals studies: All animals received humane care according to the "Guide for the Care and Use of Laboratory Animals". Experiments were performed in accordance with the UCSD IACUC and NIH guidelines. Human samples: Publicly available human database were mined. Reference:[1]PMID: 34062281

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29 | ALTERED SMALL AND LARGE INTESTINAL GENE EXPRESSION RELATED TO OXYGEN CONSUMPTION AND INFLAMMATION IN PATIENTS WITH CIRRHOSIS COULD CONTRIBUTE TOWARDS DYSBIOSIS AND LIVER DISEASE PROGRESSION★

Jing Zeng[1], Derrick Zhao[1], Andrew Fagan[2], Michael Fuchs[2], Puneet Puri[2], Brian C. Davis[2], Xuan Wang[1], Emily Gurley[1], Phillip B. Hylemon[1,3], Huiping Zhou[1,3]

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Background: Oxygen and inflammation levels in the gut have emerged as important factors in liver disease progression. Intestinal hypoxia, caused by altered blood flow and impaired oxygen delivery, triggers inflammation, and disrupts the intestinal barrier, leading to bacterial translocation and could encourage dysbiosis with facultative anaerobes. Bacterial translocation and their products reach the liver, promoting inflammation, oxidative stress, and liver damage. However, the relationship between oxygen response, gut inflammation, and liver disease progression in cirrhosis patients remains largely unknown and are the focus of this study. **Methods:** Twelve age-balanced men, including healthy control (54 ± 3 yrs), compensated (55 ± 4 yrs, MELD 7) , and decompensated cirrhosis (56 ± 5 yrs, MELD 11, prior HE on lactulose) underwent EGD & prepped colonoscopy on the same day with pinch biopsies taken from the duodenum (DUOD) and ascending colon (ASCEND). Total RNA was isolated using Trizol. Gene profiles were analyzed with the NanoString nCounter®. Differentially expressed genes (DEGs) between groups were identified using Rosalind. Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed. **Results:** Bioinformatic analysis revealed significantly upregulated expression of key inflammation-related genes [mitogen-activated protein kinase kinase 2 (MAP2K2), signal transducer and activator of transcription 3 (STAT3) and thioredoxin (TXN)], along with downregulated expression of genes associated with reactive oxygen response (ROS) [Ferredoxin 1 (FDX1), Metal Regulatory Transcription Factor 1 (MTF1)] in both DUOD and ASCEND of cirrhosis subjects compared to healthy controls. Furthermore, decompensated patients exhibited increased expression of inflammation-related genes [MAP2K1, Nuclear Factor Kappa B Subunit 1 (NFKB1) and Interleukin 6 (IL6)] and decreased ROS-related genes [Epidermal Growth Factor Receptor (EGFR) and NADH: Ubiquinone Oxidoreductase Subunit A12 (NDUFA12)] compared to compensated patients. The GO and KEGG analysis highlighted that, in compensated patients, DEGs were most associated with increase in 'aerobic respiration', 'response to hypoxia', 'oxidative phosphorylation', 'chemical carcinogenesis - reactive oxygen species' and decrease in 'response to oxidative stress', 'cellular respiration', 'inflammatory response'. Similar trends were observed in decompensated patients, with more significant changes. **Conclusion:** We found alteration in oxygen consumption-related gene expression across small and large intestine in humans with cirrhosis, which increases with progression of disease. This could promote the growth of potential anaerobic pathobionts in the gut and could be relevant in understanding the interplay between gut oxygen levels, inflammation, and liver disease in liver cirrhosis.

Table. Genes and pathways related to oxygen consumption and Inflammation in patients with cirrhosis.

Genes list	Expression in samples	Pathway included
MAP2K2, AKT1, STAT3, TXN	Upregulated significantly in cirrhosis vs controls (Duodenum part)	Inflammation including IL-1, IL-6 and TNF signaling
MAP2K2, TXN	Upregulated significantly in cirrhosis vs controls (Ascending colon part)	Inflammation including IL-1, IL-6 and TNF signaling
MAP2K1, RELA, NFKB1, IL6, RELA, NFKB1	Upregulated significantly in decompensated vs compensated (Ascending colon part)	Inflammation including IL-1, IL-6 and TNF signaling
WRN, MTF1, FDX1	Downregulated significantly in compensated vs controls (Duodenum part) Downregulated significantly in compensated vs controls (Ascending colon part)	Reactive Oxygen Response
EGFR, NDUFA12	Downregulated significantly in decompensated vs compensated (Duodenum part) Downregulated significantly in decompensated vs compensated (Ascending colon part)	Reactive Oxygen Response
NDUFA13, NDUFS7, IDH3G, NDUFA1, SDHB, SOD2, FAHD1, COX5B, SLC16A3	Upregulated significantly in cirrhosis vs controls (Duodenum part) Upregulated significantly in cirrhosis vs controls (Ascending colon part)	Mitochondrial Respiration

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The following people have nothing to disclose: Jing Zeng, Derrick Zhao, Andrew Fagan, Puneet Puri, Brian C. Davis, Xuan Wang, Emily Gurley, Phillip B. Hylemon, Huiping Zhou,
Michael Fuchs

♦ 30 | ETHANOL-INDUCED REDUCTION IN THE INTESTINAL METHYLATION POTENTIAL PROMOTES TIGHT JUNCTION DISRUPTION: PROTECTION BY BETAINE TREATMENT

Sathish Kumar Perumal[1,2], Madan Kumar Arumugam[1,2], Murali Ganesan[1,2], Natalia Osna[1], Karuna Rasineni[1,2] and Kusum K. Kharbanda[1,2], (1) Veterans Affairs Nebraska-Western Iowa Health Care System, (2)University of Nebraska Medical Center

Background: The gut-liver interaction has emerged as a critical component in alcohol-associated liver disease (ALD) pathogenesis. The central mediators are the gut

GI/Hep appointments with 1839 PS matched patients with no preoperative appointments, with covariate balance being achieved for all key covariates listed above ($p > 0.05$). Using CR, the hazard of postoperative mortality at 6 months was significantly reduced among patients who had preoperative appointments with GI/Hep + PCP (hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.36-0.88; $p = 0.01$), GI/Hep only (HR, 0.67; 95% CI, 0.46-0.96; $p = 0.02$), or PCP only (HR, 0.72; 95% CI, 0.54-0.96; $p = 0.02$) compared to those with no preoperative appointments. Similar results were obtained using FGCR analysis (Figure 1). **Conclusion:** Preoperative visits were associated with reduced risk of postoperative mortality in patients with cirrhosis, and greatest risk reduction was observed in patients with both PCP + GI/Hep visits. This suggests that these clinics may contribute to different elements of preoperative optimization that are synergistic. Future studies are needed to identify mechanisms underlying these differences to standardize preoperative optimization strategies.

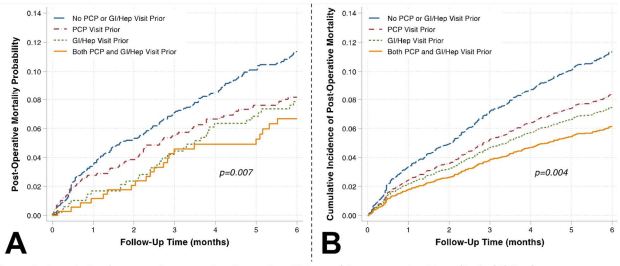

Figure 1: Association between Preoperative Outpatient Visits and Post-operative Mortality in (A) Kaplan-Meier and (B) Competing Risk Analyses in the Propensity Matched Cohort

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79 | DEVELOPMENT AND VALIDATION OF AN ALGORITHM FOR THE PREDICTION OF HIGH-RISK VARICES IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC)

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Background: An assessment of varices is required prior to systemic therapy in patients with HCC. However, current non-invasive criteria, including the Baveno criteria, have not been validated in patients with HCC, and performing an EGD can delay HCC treatment initiation. We aimed to develop a noninvasive algorithm for assessing varices in patients with unresectable HCC. **Methods:** We performed a multicenter

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retrospective study from 20 centers in the US, including adult patients with BCLC stage B/C HCC from 2007-2019. We included those with Child Pugh A5-B7 cirrhosis with an EGD within 12 months of index imaging without intervening HCC treatment. We excluded patients with history of variceal bleeding or uncontrolled ascites or hepatic encephalopathy. We collected demographics, laboratory data, and CT/MRI imaging findings extracted by an abdominal radiologist including presence of abdominal varices, spleen diameter/volume, and portal vein diameter. High-risk varices per EGD were defined as large varices, those requiring banding, presence of white nipple, or presence of red wale. We used elastic net for variable selection and model building. We divided the cohort into a 70:30 training set and validation set, with the goal of maximizing negative predictive value to avoid EGD in low-risk patients. **Results:** We included 707 patients, with a median age 64.6 years, 80.6% male and 59.8% White, 15.0% Black, 8.2% Asian, and 23.2% Hispanic. The most common liver disease etiologies were hepatitis C (43.6%), alcohol (39.9%), hepatitis B (6.5%), and NASH (4.7%). Patients were evenly distributed between BCLC B (54.0%) and C stage (46.0%) disease. Median time from HCC diagnosis to EGD was 47.4 (IQR: 114) days, with 24.4% of patients having high-risk varices. Our clinical model (Table) achieved an NPV of 87.0% in the validation cohort. Our model including imaging variables (Table) increased NPV to 93.0% in the validation cohort. The model would avoid conducting EGDs in 49 out of every 100 patients without significant varices. In a sensitivity analysis including other high risk bleeding diatheses (gastric varices and portal hypertensive gastropathy), the model had an NPV of 89%. **Conclusion:** A model using clinical and imaging data can accurately predict absence of high-risk varices in patients with HCC and avoid EGD in many patients prior to initiation of systemic therapy, thereby expediting care for patients with unresectable HCC.

Table: Predictor variables for presence of high-risk varices in patients with unresectable HCC

Model	Components	Negative Predictive Value	EGDs Avoided per 100 low risk patients	EGDs not conducted per 100 high risk patients
Clinical/Demographic Variable Model	Age, Sex, Child Pugh score, platelet count, albumin	87%	56	30
Clinical/Demographic + Radiographic Variables Model	Platelet count, AFP, ALT, spleen diameter, spleen volume, portal vein diameter	94%	49	18

Disclosures: Neehar Dilip Parikh – Eisai: Advisor, No, Yes; Exact Sciences: Consultant, No, Yes; Gilead: Advisor, No, Yes; Fujifilm Medical: Consultant, No, Yes; Freenome: Consultant, No, Yes; Exelixis: Consultant, No, No;
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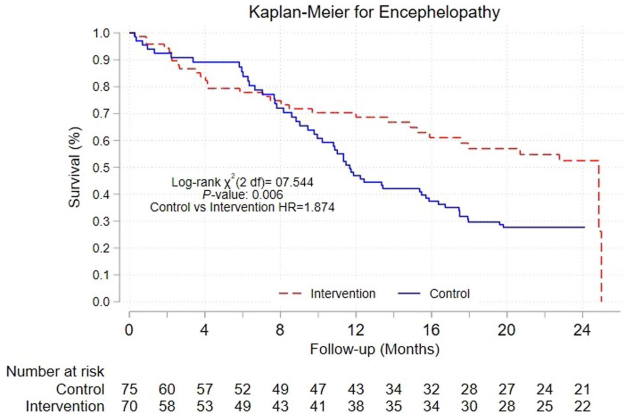
coordination model involving a nurse. Key components included intensive post-discharge monitoring (weekly phone calls for a minimum of 3 mo), rapid access to care pathway, enhanced patient and carer education and self-management support. The intervention was applied continuously for the duration of the trial. Secondary aims were to assess the effects of this model on other measures of hospital usage, mortality, patient-reported outcomes and quality of care. **Results:** 146 patients (75 Intervention group, 71 Control group) were recruited. The combined cohort had the following characteristics: mean age 54.9 years, 68% male, median MELD score 19.0 and median Child-Pugh score 9.0. The main causes of CLF were alcohol (68%), MAFLD (16%) and HCV (11%). The median (IQR) follow-up time for individual's in the Intervention and Control groups was 2.0 years. For the primary endpoint, LREA, there was a non-significant 11% reduction in LREA for the Intervention group vs. Control group (IRR 0.89, 95% CI 0.53-1.50, $p = 0.666$). Improvement trends were also seen for the Intervention group for ICU admissions (IRR = 0.62 $p = 0.491$), 7-day readmissions (IRR = 0.72, $p = 0.62$), and length of stay (IRR = 0.86, $p = 0.56$). The leading causes of LREAs were ascites (43%), encephalopathy (22%) and variceal bleeding (11%). There was an increased risk of LREA due to encephalopathy in the Control vs. Intervention group (Hazard ratio = 1.87, 95% CI = 1.18-2.96, $p = 0.007$); see Figure. There were no significant differences observed between groups for actuarial survival, or quality-of-life measures (CLDQ, EQ5D-5L utility, EQ-5D-VAS, QALY gains). All quality-of-care measures were improved in the Intervention group with significant improvement for HCC surveillance adherence ($p = 0.05$), performance of bone density ($p = < 0.001$) and vitamin D testing ($p = < 0.001$). **Conclusion:** This care coordination model showed benefits for CLF patients, particularly for reductions in LREA due to encephalopathy and improved quality of care. Further studies are needed to define this intervention model's optimal components, patient groups and settings. Further studies examining model cost-effectiveness and qualitative experiences of patients and care providers are in progress.



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84 | LIVER CANCER SURVEILLANCE IN THE VA: IMPLEMENTATION-EFFECTIVENESS STEPPED-WEDGE CLUSTER-RANDOMIZED TRIAL

Vera Yakovchenko[1], Patrick Spoutz[2], Brittney Neely[1], Carolyn Lamorte[1], Dawn Scott[3], Heather McCurdy[4], Anna Marie Nobbe[5], Nsikak Richard Ekanem[6], Gwen Robins[7], Jasmohan S. Bajaj[8], Monica Merante[1], Sandra Gibson[1], Chaeryon Kang[9], Tamar H. Taddei[10,11], Timothy R. Morgan[12] and Shari S. Rogal[1,9], (1)VA Pittsburgh Healthcare System, (2)Veterans Integrated Service Network 20, (3)Central Texas VA Healthcare System, (4)VA Ann Arbor Healthcare System, (5) Cincinnati VA Medical Center, (6)VA Northern Indiana Healthcare System, (7)Martinsburg VA Medical Center, (8)Virginia Commonwealth University and Central Virginia Veterans Healthcare System, (9)University of Pittsburgh, (10)Yale University, New Haven, CT, (11) West Haven VA Medical Center, (12)VA Long Beach Healthcare System

Background: AASLD and EASL guidelines recommend all people with cirrhosis undergo twice yearly screening for hepatocellular carcinoma (HCC) with hepatic imaging. However, patient, provider, and system level barriers impede ongoing surveillance efforts. This stepped-wedge hybrid effectiveness-implementation trial assessed the impacts of using a quality improvement playbook called Getting to Implementation (GTI) to support VA facilities to select, implement, and evaluate data-driven strategies to improve HCC surveillance. **Methods:** This hybrid type III (implementation-effectiveness) stepped-wedge cluster randomized design was conducted at 12 VA sites between October 2020 and April 2023. We used a multi-faceted facilitation strategy consisting of manualized GTI during a 12-month active implementation and six-month sustainment period. The primary implementation outcome was GTI completion and strategy implementation. The secondary clinical outcome was receipt of guideline-concordant HCC surveillance at baseline, post-intervention, and sustainment. Analysis involved a three-level, generalized linear mixed model. **Results:** Of 12 VA facilities, selected based on having low baseline HCC surveillance rates, 10 completed GTI with high fidelity. These 10 sites implemented a median of four implementation strategies while receiving an average of 19 ± 5 facilitation hours. HCC surveillance improved from 21% at baseline to 30% during

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intervention and remained elevated at 32% during sustainment. Sites receiving more facilitation ($r = 0.59$, $p = 0.048$) and sites implementing a greater variety of strategies had higher HCC surveillance improvement. Generalized linear mixed models indicated significant changes in HCC surveillance during both implementation (aOR = 1.306; 95% CI: [1.159, 1.472], $p < 0.0001$) and sustainment (aOR versus control = 1.511; 95% CI: [1.315, 1.73], p-value < 0.0001). Sustainment, a challenge for implementation trials, was significantly associated with improvement in HCC surveillance compared with active implementation (aOR = 1.168; 95% CI: [1.018, 1.340], p-value 0.0271). **Conclusion:** Data-driven strategies with facilitated quality improvement sustainably improved HCC surveillance in Veterans with cirrhosis receiving care in the lowest-performing VA facilities. Further research is needed to understand the heterogenous effects across sites, which may have been driven by differences in site baseline characteristics and facilitation and strategy implementation nuances.

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85 | FEASIBILITY AND RESULTS OF AN INPATIENT TELEHEPATOLOGY CONSULT SERVICE IN AN INTEGRATED HEALTH SYSTEM

Haleigh Hanson[1], Loren Cihlar[1], Amber Rutues[1], Hollie Mayes[1], Niharika R. Samala[2], Samer Gawrieh[3], Craig Lammert[4], Howard C. Masuoka[5], Naga P. Chalasani[6] and Raj Vuppalanchi[4], (1)Indiana University Health, (2) Indiana University, Indianapolis, IN, (3)Indiana University School of Medicine, Indianapolis, IN, (4)Indiana University School of Medicine, (5)Indiana University, (6) Indiana University Medical Center, Indianapolis, IN

Background: Providers at community hospitals often seek to transfer hospitalized patients with advanced liver disease to tertiary/quaternary care hospitals for further management due to lack of expertise in caring for these patients. However, it is possible to co-manage such patients at local hospitals by providing virtual consultation by tertiary care hepatologists via inpatient telehepatology (INP-TH) consultation. We aimed to describe demographics, liver disease severity, and related outcomes such as transfer rate, subsequent outpatient follow-up, readmission rate, and 30-day mortality. **Methods:** Indiana University Health (IUH) is a 16-hospital integrated health system with a single adult academic health center (AAHC) with concentrated hepatology expertise and a liver transplant program. We established a pilot INP-TH team led by a Hepatologist, an Advanced Practice Provider, and a Medical Assistant in July 2022 to co-manage hospitalized patients with advanced liver disease at an affiliated IUH community hospital. In this model, providers caring at the community IUH hospital request a telemedicine consultation from INP-TH team in lieu of a hospital transfer. American Well platform embedded with Cerner's electronic health record (EHR) with a patient facing Apple iPad was utilized for the current study. **Results:** A total of 81 INP-TH consultations were provided, with only 9 (11%) patients requiring a transfer to the AAHC. Of these 81 consultations, 66 consultations on 61 unique patients had outcomes data with greater than 30-day follow-up. The median age was 60 (range: 19-80) years with 65% having a diagnosis of cirrhosis. At the time of INP-TH consult, 80% had signs of liver decompensation with MELD 21 $\pm$ 7; 83% had MELD $\geq$15. The more common etiologies of liver disease included alcohol associated liver disease (30%) and non-alcoholic fatty liver disease (29%). The duration of hospitalization was 9.2 $\pm$ 8.3 days with duration of stay 3.2 $\pm$ 3.9 days prior to INP-TH consultation. There were 20 (30%) patients requiring readmission. Thirty (45%) patients who were not transferred were seen in the outpatient setting at AAHC within 30 days. In 61 patients

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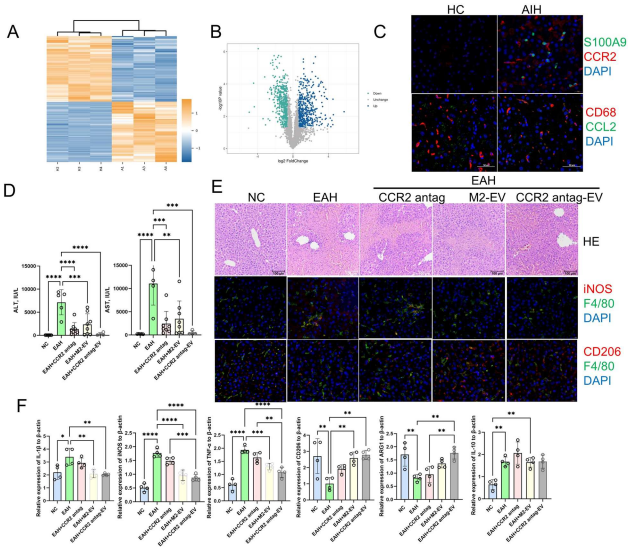

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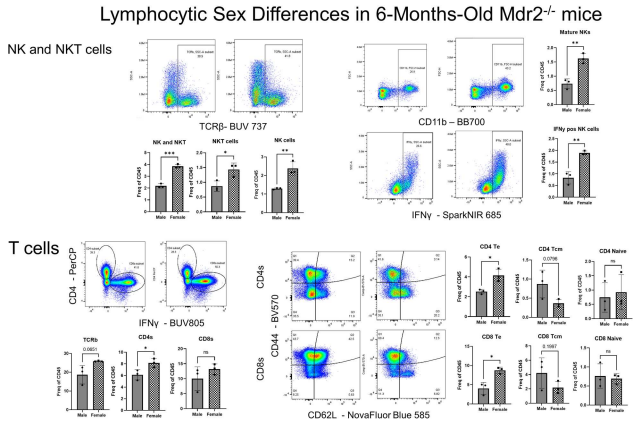
109 | IMMUNOLOGICAL PROFILE ASSOCIATED WITH SEX DISPARITY OF CHOLESTATIC LIVER INJURY IN Mdr2-/- MICE

Grayson Way[1], Jing Zeng[2], Yun-Ling Tai[3], Derrick Zhao[3], Xixian Jiang[3], Xuan Wang[3], Rebecca Martin[1], Phillip B. Hylemon[3] and Huiping Zhou[1,3,4,5], (1)Virginia Commonwealth University, (2)Department of Microbiology and Immunology, Medical College of Virginia and Mcguire Veterans Affairs Medical Center, Virginia Commonwealth University, Richmond, VA, United States, (3)Department of Microbiology and Immunology, Medical College of Virginia and Mcguire Veterans Affairs Medical Center, Virginia Commonwealth University, Richmond, VA, (4)Stravitz-Sanyal Institute for Liver Disease & Metabolic Health, School of Medicine, Virginia Commonwealth University, Richmond, VA, USA, (5)Central Virginia VA Health Care System

Background: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by inflammation, bile duct proliferation, and hepatic fibrosis, with a high risk for liver cancer. Multi-drug resistance 2-deficient ($Mdr2^{-/-}$) mice have been widely used as a PSC model. These mice spontaneously develop fibrosis as early as 6-8 weeks and liver tumors at 10-12 months. Previous studies from our lab, and others, have shown that female $Mdr2^{-/-}$ mice have worse disease progression with increased tumor burden compared to male $Mdr2^{-/-}$ mice. However, the specific immunological landscape underlying sex differences in disease progression in $Mdr2^{-/-}$ mice remains unclear and is the focus of this study. **Methods:** Age and sex-matched wild type (WT) and $Mdr2^{-/-}$ mice (FVB, 3-12 mo, n = 6-12) were used. Brefeldin A was injected via the tail vein 3-6 hours prior to liver perfusion. The livers were then isolated, digested, and processed into a single-cell suspension. After removing the hepatocytes, the immune cells were fixed, incubated with Fc blocker and stained with cell-type-specific antibodies, and run on a Cytek Aurora spectral flow cytometer. All cells are pre-gated on live-dead gating by Zombie-UV, singlet gating, and CD45+ gating. The mRNA expression levels of key genes involved in inflammation and fibrosis were measured by qPCR. Liver injury was assessed by histology. **Results:** Total macrophages and Kupffer cells (KCs) were significantly reduced, while T cells and PMN-MDSCs were increased in $Mdr2^{-/-}$ mice compared to WT in both genders at 3-5 months old. At both 6 and 12 months old, male $Mdr2^{-/-}$mice have stronger macrophage-focused immune responses, with more total macrophages and monocyte-derived macrophages (Md-MQs) than females, while female $Mdr2^{-/-}$ mice have higher lymphocyte response than male mice with more CD4s, CD4Tes, Th1s, Th2s, Tregs, CD8Tes cells. However, the sex difference in NK and NKT cells was only identified in 6-month-old $Mdr2^{-/-}$ mice; females have higher NKs, NKTs, mature NKs, and IFNy-positive NK cells. qPCR analysis revealed that 12-month old female $Mdr2^{-/-}$mice have significantly higher expression of Cxcl16, Cxcl10, Cxcl12, Cxcr4, Cxcr6, Ck19, Col1a1 and Col4a1, etc. **Conclusion:** Identification of the specific immunological landscape associated with the sex disparity of $Mdr2^{-/-}$ mice in cholestatic liver injury and tumorigenesis will provide valuable insights into the pathogenesis of PSC and develop sex-specific therapeutics.



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Derrick Zhao, Xixian Jiang, Xuan Wang, Phillip B. Hylemon, Huiping Zhou
Disclosure information not available at the time of publication: Rebecca Martin

110 | B CELL ACTIVATION IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS: METABOLIC SHIFTS AND IMPLICATIONS FOR ANTIGEN-SPECIFIC RESPONSES

Fanta Barrow, University of Minnesota

Background: Metabolic dysfunction associated steatohepatitis (MASH) involves immune mechanisms and the contribution of adaptive immunity to disease progression has been increasingly recognized. B cells, with their ability to modulate inflammation, are key players in inflammatory diseases. However, their precise role and underlying mechanisms in MASH pathogenesis remain unclear. Therefore, our research aims to investigate the mechanisms driving B cell activation and their pro-inflammatory activity in MASH. **Methods:** We established a mouse model of MASH by feeding mice a high-fat, high-carbohydrate diet to closely resemble human MASH. We focused on studying the secretome of B cells by employing Isoplexis single-cell B cell secretome analysis specifically on intrahepatic B cells from mice with MASH and healthy controls. To understand the phenotypic landscape of liver B cells during MASH, single-cell RNA sequencing was used to characterize their transcriptional profiles. Metabolic adaptations of B cells during MASH were explored using Seahorse XF assays and targeted metabolomics. To investigate the role of B cell antigen-specific responses in MASH, B cell receptor restricted mice fed the MASH-inducing diet were utilized. **Results:** Our investigation revealed a notable accumulation of pro-inflammatory B cells in the livers of MASH patients and mice fed a high-fat, high-carbohydrate diet. Single-cell B cell secretome analysis uncovered a proteomic landscape reflecting their pro-inflammatory function. Additionally, single-cell RNA sequencing identified a population of immature B cells that diminished during MASH, indicating altered maturation. We hypothesized that metabolic regulation might be involved due to these changes. Seahorse XF assays showed that B cells in MASH rely on increased oxidative phosphorylation (OXPHOS) rather than glycolysis for energy during immune activation. Importantly, we found that OXPHOS-dependent ATP production is fueled by pyruvate oxidation. Inhibiting pyruvate oxidation in MASH B cells completely abolished their pro-inflammatory potential, dependent on B cell receptor signaling. B cell receptor-restricted mice, recognizing an irrelevant antigen, displayed improved disease outcomes with enhanced fatty acid β-oxidation, decreased steatosis, and reduced fibrosis. Additionally, disease amelioration was accompanied by systemic decreases in IgG antibody isotypes, previously correlated with MASH severity in humans. **Conclusion:** Our study highlights the pro-inflammatory role of B cells in MASH, driven by metabolic adaptations and antigen-specific responses. Understanding the factors regulating B cell metabolism during inflammation could open avenues for selectively targeting their pathogenic activity in MASH.
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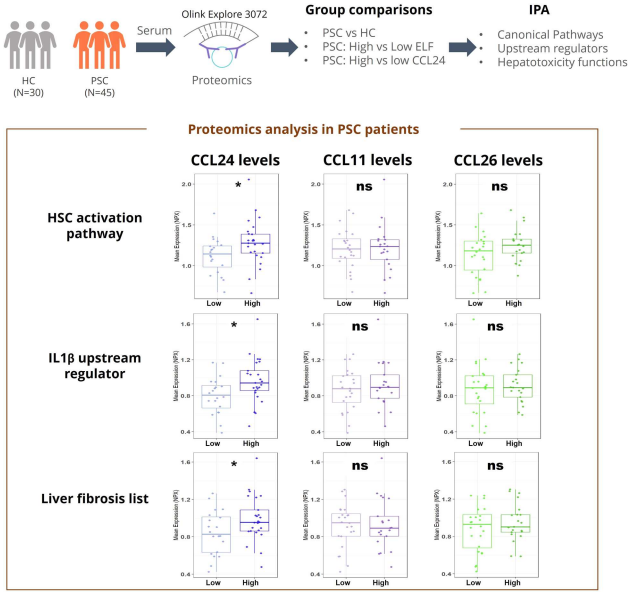
111 | SERUM PROTEOMICS REVEALS UNIQUE ASSOCIATION OF CCL24 WITH DISEASE-RELATED PATHWAYS AND SIGNATURES IN PRIMARY SCLEROSING CHOLANGITIS

Ilan Vaknin[1], Tom Snir[1], Raanan Greenman[1], Revital Aricha[1], John Lawler[1], Francesca Saffioti[2,3], Douglas Thorburn[2], Massimo Pinzani[2] and Adi Mor[1], (1) Chemomab Ltd., (2)UCL Institute for Liver and Digestive Health, University College of London, (3) Oxford University Hospitals NHS Foundation Trust

Background: Primary sclerosing cholangitis (PSC) is a chronic liver disease characterized by inflammation and fibrosis of the bile ducts. CCL24 (Eotaxin-2) is a chemokine that promotes inflammation and fibrosis and is overexpressed in the liver of patients with PSC, particularly in areas with biliary injury. Previous studies showed that blocking CCL24 interferes with core pathways that contribute to PSC pathophysiology in preclinical models. These properties are unique to CCL24 and are not shared with other ligands of its cognate receptor, CCR3, like Eotaxin-1 (CCL11) and Eotaxin-3 (CCL26). In this study, we aim to further investigate the unique role of CCL24 in the pathophysiology of PSC and its association with disease-related pathways. **Methods:** Sera from patients with PSC (n = 45) and healthy controls (n = 30) were analyzed using the Olink proximity extension assay (PEA) of 3072 proteins. Subjects' demographics and enhanced liver fibrosis (ELF) score were documented. Serum proteomics data were analyzed according to three comparisons: (1) healthy controls vs. patients with

PSC, (2) fibrosis severity in PSC patients, defined by ELF score (9.8 cutoff, defining advanced fibrosis), and (3) serum levels of CCL24 in PSC patients. Differentially expressed proteins (DEPs) were subjected to Ingenuity Pathway Analysis. Expression of protein lists was compared between healthy controls and patients with PSC, then further analyzed among patients with PSC, stratified by serum levels of CCL24, CCL11 or CCL26. **Results:** Serum proteomics analysis revealed canonical pathways (such as hepatic stellate cell activation) and upstream regulators (such as IL1β) which are activated in patients with PSC, in patients with advanced fibrosis and in patients with high CCL24 levels. Additionally, protein lists related to multiple hepatotoxicity functions, such as liver fibrosis, were upregulated in patients with high CCL24 levels. Furthermore, expression of these protein lists was found to be uniquely associated with serum levels of CCL24, but not associated with CCL11 or CCL26. **Conclusion:** This study provides further evidence of the critical role of CCL24 in the pathogenesis of PSC, highlighting its unique association with disease-related pathways not shared by other eotaxins. Targeting CCL24 could be a promising therapeutic strategy for the treatment of PSC, which supports the ongoing phase 2 study of CM-101, a CCL24 neutralizing antibody, in patients with PSC.



Disclosures: Ilan Vaknin – Chemomab ltd: Employee, Yes, No;
Tom Snir – Chemomab: Employee, Yes, No;
Raanan Greenman – Chemomab: Employee, Yes, No;
Revital Aricha – Chemomab: Employee, Yes, No;
John Lawler – Chemomab: Employee, Yes, No;
Massimo Pinzani – Chemomab: Consultant, Yes, No;
Adi Mor – Chemomab: Employee, Yes, No; Chemomab: Executive role , Yes, No;
The following people have nothing to disclose: Francesca Saffioti, Douglas Thorburn

112 | RUNX1 TRANSCRIPTION FACTOR MEDIATES THE TGFβ-STIMULATED INFLAMMATORY RESPONSE BY CHOLANGIOCYTES IN PRIMARY SCLEROSING CHOLANGITIS

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Background: Primary sclerosing cholangitis (PSC) is marked by inflammation and progressive biliary fibrosis, which can lead to cirrhosis and its complications. Cholangiocytes activated by transforming growth factor-β (TGFβ) signal to immune cells and activate hepatic myofibroblasts to deposit the extracellular matrix. Our previous data suggest that TGFβ-mediated transcriptomic changes in cholangiocytes may occur through runt-related transcription factors (RUNX). However, studies of RUNX1 in hepatobiliary fibrosis have revealed conflicting findings because of unexplored mechanistic understanding in cholangiocytes, which is the focus of this study. **Methods:** Mouse large biliary epithelial cells (MLE) and PSC-derived cholangiocytes (PSC-C) were used to test the effects of RUNX inhibitors (Ro5-3335 and AI-10-104) and siRNA knockdown on TGFβ-mediated signaling. Multidrug resistance 2 deleted ($Mdr2^{-/-}$) mice (12 weeks, male and female) were treated with the RUNX inhibitor Ro5-3335 intraperitoneally at 50 mg/kg every other day for 3 weeks. **Results:** RUNX1 mRNA is significantly increased in TGFβ-treated cholangiocytes, $Mdr2^{-/-}$ mouse cholangiocytes and RNA-seq of PSC tissue (Log Fc 1.63) (GEO data set: GSE159676). RUNX inhibitors significantly reduced the expression of fibroinflammatory markers such as platelet-derived growth factor B (PDGFB) and interleukin 6 (IL-6) in TGFβ treated MLE. Ro5-3335, also reduced the basal expression of PDGFB and IL-6

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in PSC-C. RUNX1 specific siRNA knockdown in PSC-C reduced the basal expression of IL-6. Conversely, the expression of anti-inflammatory and anti-fibrotic, peroxisome proliferator-activated receptor γ (PPARγ) was increased. Mdr2$^{-/-}$ mice treated with Ro5-3335 showed significant reductions in serum alanine transaminase and hepatic expression of inflammatory markers (Il-6, Tnfa, Il-1b, Nfkb) by 40-75% but not the anti-inflammatory cytokine, Il-10. In contrast, mRNA markers (Collagen, α-Smooth muscle actin) and picrosirius red histological staining of fibrosis did not show a significant reduction. **Conclusion:** RUNX1 has an essential role in TGFβ-mediated activation of the inflammatory response in cholangiocytes and Mdr2$^{-/-}$ mice. We are conducting longer *in vivo* experiments of RUNX inhibition to determine the effects on biliary fibrosis. Cholangiocyte-selective RUNX1 knockout mice will also be used for further investigation. Targeting RUNX1 may represent a novel therapeutic strategy in cholestatic liver disease.

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113 | ESTABLISHMENT OF PFIC 3 MOUSE MODEL CARRYING HUMAN-LIKE BILE ACID COMPOSITION BY IN VIVO LIVER-SPECIFIC GENE DELETION USING ADENO-ASSOCIATED VIRUS AND CRISPR/Cas9 SYSTEM

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Background: There are very limited high-quality data from which to derive therapeutic approaches to portal hypertension (PHT) in children. Management of varices, in particular, is quite controversial in pediatrics. IMPPHR was developed to derive large-scale international data, thereby enhancing our knowledge of PHT. The three major foci of data collection in IMPPHR are, 1) morbidity and mortality of first variceal hemorrhage, 2) feasibility and safety of primary prophylaxis of varices, 3) approaches to secondary prophylaxis of variceal hemorrhage. Subject level data collection is ongoing in IMPPHR (n = 241 cases as of 4.27.23) and will be reported in the future. This report provides center-specific data relevant to the management of varices. **Methods:** Each site submitted institutional resources and clinical activity accrued over 2 years between January 1, 2018 and December 31, 2019 to present a snapshot of resources and approaches available in clinical practice. **Results:** 23 centers (11 countries, 4 continents) serving an aggregate population of > 100,000,000 with 5970 hospital beds and 1024 ICU beds provided site specific data. Overall 600 liver transplants were performed at the sites for indications that included but were not limited to PHT ([median per center] 19: [25-75%ile] 6-34) of which 112 (1: 0-6) were living donor and 222 (5: 0-10) were technical variant grafts. In aggregate, 885 (23: 15-38) endoscopic variceal ligations were performed by 99 (4:2-6) individual's, while 266 (3:0–10) endoscopic sclerotherapy sessions were performed by 46 (2: 0-3) individual's. Potential two year endoscopic practitioner caseload varied significantly by site (variceal ligation 7: 2.8-13.8, sclerotherapy 1.5: 0.0-5.0). Nontransplant nonendoscopic interventions for PHT included 55 (range per center 1–20) portosystemic shunts (12/23 centers), 21 (range 1–5) TIPS (8/23 centers) and 30 (range 1–8) MesoRex bypass procedures (11/23 centers). 8 centers, Group A, performed at least 3 of at least one of these nontransplant nonendoscopic procedures; their center characteristics differed from the remaining 15 centers, Group B (Table). **Conclusion:** A multi-center registry focused on pediatric esophageal varices, has been developed with ongoing patient data entry. Site specific data reveals marked variability in approaches. Many pediatric centers perform only small numbers of endoscopic procedures for PHT, often divided among several proceduralists. There is also variable and limited use of nonendoscopic nontransplant interventions for PHT. IMPPHR will permit analysis of the impact of differences in approach on outcomes, helping to inform optimal treatment decisions and program planning. Supported by the Spain Family and an ESPGHAN Networking Grant.

Characteristic ->	Population of area (M)	Hospital Beds	OLT	LRD	Tech Variant	EVL	EST
Group A (n = 8)	7.3 ± 4.8	259 ± 168	38.5 ± 34.0	7.2 ± 6.9	20.5 ± 29.4	65.8 ± 68.7	22.6 ± 25.2
Group B (n = 15)	2.8 ± 2.7	259 ± 130	19.5 ± 22.0	3.6 ± 7.5	3.9 + 4.8	23.9 ± 14.0	5.7 ± 11.9
p-value	0.009	1.000	0.118	0.273	0.041	0.031	0.039

Group A – at least 3 MesoRex Bypass, Portosystemic Shunt or TIPS, Group B – the rest
* mean ± standard deviation, M = million, OLT = orthotopic liver transplant, LRD = living related donor, Tech variant = technical variant graft, EVL = endoscopic variceal ligation, EST = endoscopic sclerotherapy

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135 | PNPLA3 GENOTYPES ARE SIGNIFICANTLY ASSOCIATED WITH LIVER-RELATED OUTCOMES IN INDIVIDUALS WITH BIOPSY-PROVEN NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Naga P. Chalasani[1], Eduardo Vilar[1], Katherine Yates[2], Arun Sanyal[3], Rohit Loomba[4], Brent Neuschwander-Tetri[5], Kris V. Kowdley[6], Anna Mae Diehl[7], Srinivasan Dasarathy[8], Norah Terrault[9], Laura Wilson[2] and James

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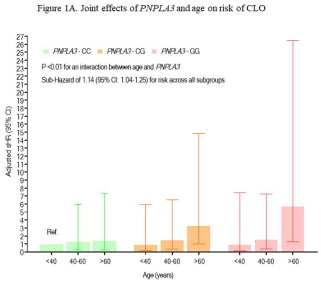
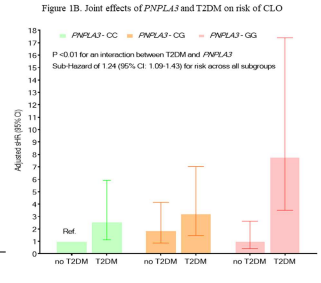
Background: The effect of *PNPLA3* rs738409 I148M variant (G allele) on the clinical course of adults with biopsy-proven nonalcoholic fatty liver disease (NAFLD) has not been prospectively investigated. We examined (1) the association between *PNPLA3* G allele and clinical outcomes and (2) how relationships among *PNPLA3* G allele, age, and type 2 diabetes mellitus (T2DM) impact clinical outcomes in patients with biopsy-proven NAFLD. **Methods:** A total of 2,075 adults with biopsy-proven NAFLD were enrolled in the NASH CRN studies between October 2004 and May 2019, and prospectively followed until September 2020, death, or transplant. Cox proportional and competing risk models were used to examine associations between *PNPLA3* G allele and all-cause mortality (death of any cause) or composite liver (liver-specific deaths or new-onset varices, hepatic decompensation, HCC, or liver transplant)-, cardiovascular (cardiovascular or cerebrovascular-specific events or deaths)-, non-HCC malignancies (cancers-specific events, and mortality, excluding HCC)-, and chronic kidney disease (CKD) (new onset glomerular filtration rate < 60 mL/min/1.73 m^2, or CKD-related death)-related outcomes. All analyses were adjusted by race/ethnicity, age, sex, T2DM, body mass index (kg/m^2), hypertension, and smoking status. **Results:** The *PNPLA3* genotypes were CC: 32%; CG: 44%; and GG: 24%. During a median follow-up of 3.4 years, there were 53 (3%) deaths of any cause. *PNPLA3* G allele was not associated with all-cause mortality (Adj. HR: 0.85, 95% CI: 0.57-1.27), but it was significantly associated with an increased risk of the composite liver outcome (CLO) (Adj. sHR: 1.39, 95% CI: 1.06-1.81). *PNPLA3* G allele was also not associated with cardiovascular events (Adj. sHR: 1.09, 95% CI: 0.86-1.39), non-HCC malignancies (Adj. sHR: 1.00, 95% CI: 0.72-1.40) or CKD (Adj. sHR: 1.25, 95% CI: 0.90-1.74). The effect of *PNPLA3* G allele on the risk of CLO increased positively and exponentially among those aged > 60 years or with T2DM (p values for interactions < 0.01). Adults 60 or older with CG (Adj. sHR: 3.3, 95% CI: 1.0-14.8) and GG (Adj. sHR; 5.8, 95% CI: 1.3-26.5) genotypes showed the highest risk of CLO as compared to those with CG/GG genotypes and aged < 60 (Figure 1A). Similarly, T2DM patients with *PNPLA3* CG (Adj. sHR: 3.2, 95% CI: 1.5-7.0) and GG (Adj. sHR: 7.8, 95% CI: 3.5-17.4) exhibited the highest risk of CLO compared to non-T2DM people with CG/GG genotypes (Figure 1B). **Conclusion:** The carriage of *PNPLA3* G allele is associated with worse liver outcomes in patients with biopsy-proven NAFLD. Increasing age and type 2 diabetes amplify this relationship. Routine genotyping of PNPLA3 in patients with NAFLD is warranted.





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Anna Mae Diehl – Inventiva: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Tune Therapeutics: Advisor, No, No; NGM: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Hanmi: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; TARGET-NASH: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Boehringer-Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Hepta Bio: Advisor, No, No;
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136 | ADIPOSE TISSUE INSULIN RESISTANCE AFFECTS LIVER MITOCHONDRIAL FUNCTION INDEPENDENTLY OF LIVER FAT ACCUMULATION★

Fernando Bril[1], Srilaxmi Kalavalapalli[2], Kenneth Cusi[2] and Meagan Gray[1], (1)University of Alabama at Birmingham, (2)University of Florida

Background: The mechanisms contributing to the progression to NASH in patients with NAFLD are unclear. Our central hypothesis is that the inability of hepatic mitochondria to enhance nutrient oxidation in the setting of nutrient oversupply plays a key role in the progression of liver disease in NAFLD. The aim of this study was to explore the relationship between adipose tissue insulin resistance (IR), liver fat, and *in vivo* hepatic mitochondrial function. **Methods:** Patients with BMI $\geq$ 25kg/m^2, without diabetes were included in the study. Patients underwent a 2-hour oral glucose tolerance test (OGTT) and a liver proton magnetic resonance spectroscopy (^{1}H-MRS) to measure liver fat. Adipose tissue IR was estimated during a fasting period as AdipoIR: fasting insulin x free fatty acids (FFA) and in the postprandial period as insulin-mediated suppression of FFA during an OGTT. *In vivo* hepatic mitochondrial ATP levels were measured by phosphorus (^{31}P)-MRS at baseline and every 30 minutes during a 2-hour oral fructose (75 grams) challenge (OFC). Due to unregulated phosphorylation of fructose upon entering hepatocytes, the OFC

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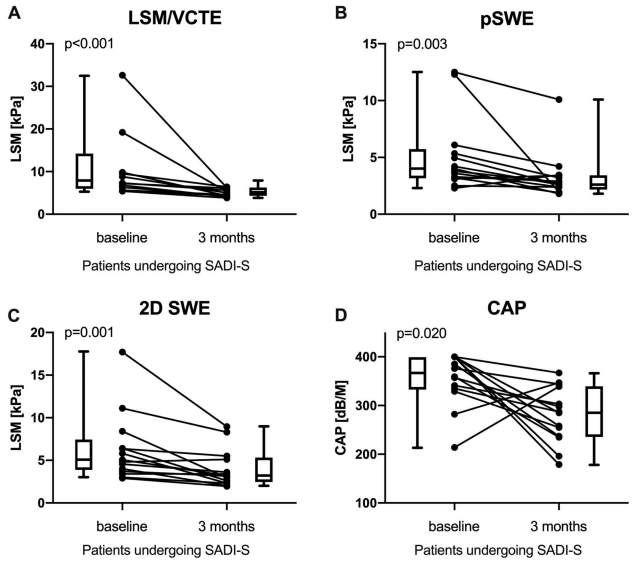
decrease in LSM and CAP are 'just' due to EWL or will translate into improved clinical outcomes.



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143 | DIGITAL IMAGE QUANTIFICATION OF THE ANTIFIBROTIC EFFECT OF SEMAGLUTIDE AND THE IMPACT OF LIVER FAT IN NONALCOHOLIC STEATOHEPATITIS

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Background: Following reductions in steatosis and body weight with glucagon-like peptide-1 receptor agonist treatment for nonalcoholic steatohepatitis (NASH), decreases in liver volume can cause collagen condensation resulting in an over estimation of fibrosis burden when measured by pathologist-reported histology evaluation. Thus, improved methods to objectively evaluate histological changes are needed. Here, digital quantification of the collagen proportionate area (CPA) was compared in the total biopsy area and non-steatotic liver tissue (fat-free CPA) following semaglutide treatment for NASH. **Methods:** This was a post-hoc exploratory analysis of a phase 2 randomized trial of subcutaneous semaglutide 0.1, 0.2, or 0.4 mg once daily versus placebo (NCT02970942). Patients had biopsy-confirmed NASH and fibrosis stage F1–F3. Liver biopsies were obtained up to 21 weeks before screening

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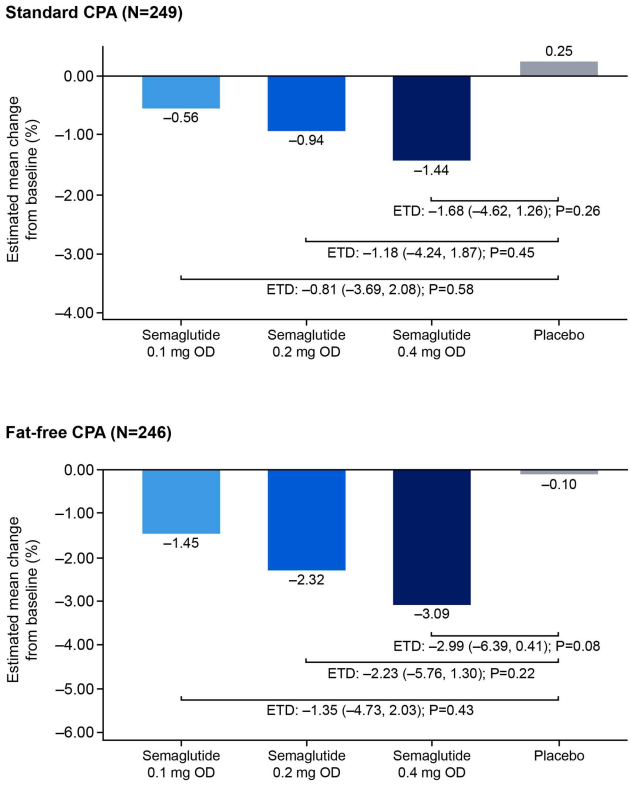
or at baseline and at week 72; digitized biopsy slides were evaluated. CPA was quantified by measuring collagen deposition as a proportion of either: 1) the total biopsy area (standard CPA) or 2) the non-steatotic biopsy area (i.e. normalized for fat: fat-free CPA = collagen area / [biopsy area – steatosis area]). Changes from baseline to week 72 were analyzed by analysis of covariance for both methods. **Results:** Digitized slides were available for 249 patients for the standard CPA analysis, and 246 patients for the fat-free CPA analysis. A dose-dependent semaglutide treatment effect was seen with both methods (Figure). Standard CPA was numerically reduced with semaglutide 0.4 mg vs placebo (estimated treatment difference [ETD]: –1.68 [95% confidence interval: –4.62, 1.26]; $p = 0.26$). For fat-free CPA, the semaglutide 0.4 mg ETD increased to –2.99 (95% confidence interval: –6.39, 0.41), and the *p*-value approached statistical significance ($p = 0.08$). An enhanced reduction of CPA was seen across all semaglutide doses when measured by fat-free versus standard CPA (Figure). **Conclusion:** When measuring CPA before and after semaglutide treatment, the removal of the confounding effect of the fat area results in numerically greater improvements in fibrosis. The fat-free adjustment analysis for CPA increases the accuracy of fibrosis resolution assessment when using drugs with strong anti-steatogenic effects.

Change from baseline to week 72 in standard and fat-free CPA



CPA, collagen proportionate area; ETD, estimated treatment difference; OD, once daily; sema, semaglutide

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148 | TRIPLE HORMONE RECEPTOR AGONIST RETATRUTIDE RESOLVES STEATOSIS IN > 85 % OF SUBJECTS WITH MASLD AND OBESITY IN ASSOCIATION WITH IMPROVED METABOLIC HEALTH

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Background: Retatrutide (RETA; LY3437943) is a novel triple agonist of the GIP, GLP-1 and glucagon receptors under investigation for obesity treatment. A 48-week phase 2 obesity study demonstrated weight loss of −22.8% and −24.2% with RETA 8 and 12 mg. We report effects of RETA on liver fat (LF) and correlations with metabolic measures in subjects with MASLD included in this trial. **Methods:** Adults aged 18-75 yr with BMI ≥30 or ≥27 kg/m^2 and ≥1 weight-related condition (T2D excluded) were randomly assigned to 48 wk of QW sc RETA (1, 4, 8 or 12 mg) or PBO. The MASLD substudy included subjects with ≥10% LF (MRI-PDFF). The primary outcome was relative LF change from baseline (CFB) at 24 wks. Additional outcomes included relative LF CFB at 48 wks and proportion of subjects achieving LF < 5%. Relationships between relative LF CFB and changes in body weight (BW), waist circumference (WC) and fasting metabolic biomarkers were explored. **Results:** Of 338 subjects enrolled in the trial, 98 (46.9% female) participated in the substudy with mean age 46.6 yrs, BMI 38.4 kg/m^2, WC 118.3 cm, ALT 35.9 IU/L, AST 25.4 IU/L, FIB4 0.79 and ELF 8.1. Mean LF at baseline ranged from 15.6 to 21.0% across treatment groups. The mean relative LF CFB (%) at 24 wks was −42.9 (RETA 1 mg), −57.0 (4 mg), −81.4 (8 mg), -82.4 (12 mg) and +0.3 (PBO), and at 48 wks was −51.3 (1 mg), −59.0 (4 mg), −81.7 (8 mg), −86.0 (12 mg) and −4.6 (PBO) (all $p < 0.001$ vs PBO). At 48 wks, LF < 5% was achieved by 57% (1 mg), 29% (4 mg), 89% (8 mg), 93% (12 mg) and 0% (PBO) of subjects (all $p < 0.001$ vs PBO). ALT and AST did not change consistently versus PBO. At 48 wks, relative LF reduction was significantly correlated with %CFB in BW and WC (r = 0.774 and 0.588, respectively; both $p < 0.001$); a nonlinear relationship with BW %CFB was demonstrated, with near-maximal LF reduction achieved at ~20% BW loss ($p = 0.002$; Figure). RETA doses ≥ 4mg improved insulin sensitivity, reflected by significant reductions vs PBO for fasting insulin (range -37.3 to -70.9%), HOMA2-IR (insulin; -35.8 to -69.3%), and increases vs PBO for adiponectin (29.8 to 99.3%) at 24 and 48 wks (all $p < 0.05$). By 24 wks, RETA doses ≥4mg significantly changed biomarkers of lipid storage and metabolism vs PBO ($p < 0.05$), including reducing triglycerides (TG; range -35.4 to -40.0%), leptin (-29.0 to -55.8%), and FGF-21 (-52.2 to -65.7%), and increasing beta-hydroxybutyrate (BOHB; 78.0 to 181.2%), a marker of fatty acid oxidation. At 24 and 48 wks, significant ($p < 0.05$) linear correlations were observed between relative LF reduction and % CFB in liver volume, TG, insulin, HOMA2-IR, adiponectin, leptin and FGF-21, but not BOHB. **Conclusion:** In subjects with MASLD, RETA 8 and 12 mg resolved steatosis in > 85% of subjects. Near-maximal LF reductions were achieved at ~20% reductions in BW. LF reductions were linearly related with metabolic measures associated with improved insulin sensitivity and lipid metabolism.

Figure 1 - Scatterplot and fitted power model curve between the relative liver fat reduction vs. percent changes in body weight at Week 48.

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149 | RELATIONSHIP OF NON-INVASIVE MEASURES WITH HISTOLOGICAL RESPONSE IN PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS AND FIBROSIS: 52-WEEK DATA FROM THE PHASE 3 MAESTRO-NASH TRIAL

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Background: MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy-confirmed non-alcoholic steatohepatitis (NASH) and fibrosis. 966 patients with biopsy-confirmed NASH were randomized 1:1:1 to resmetirom 80mg, resmetirom 100mg, or placebo administered once daily. Histologic endpoints were assessed after 52 weeks. Dual primary endpoints at Week 52 were achieved with both resmetirom 80mg and 100mg: NASH resolution with no worsening of fibrosis (NR) or $\geq$1-stage reduction in fibrosis with no worsening of NAS (FR). **Methods:** Adults with $\geq$3 metabolic risk factors, liver stiffness $\geq$8.5 kPa, hepatic fat $\geq$8%, biopsy-confirmed NASH with F1B-F3 fibrosis, and NAS $\geq$4 were eligible to participate in MAESTRO-NASH. The relationship of non-invasive measures with histological response (NR and/or FR) in the resmetirom 80mg, resmetirom 100mg, and placebo groups was assessed. **Results:** Patients with biopsy-confirmed NASH with fibrosis had high metabolic risk including obesity (mean BMI = 36), type 2 diabetes (70%), hypertension (78%), and 10-year ASCVD risk score > 14. Baseline mean (SD) FibroScan VCTE was 13.3 (6.8), 13.6 (7.1), and 12.9 (5.6) kPa for the resmetirom 80mg, resmetirom 100mg, and placebo groups. Baseline ELF across all fibrosis groups was 9.8 (0.87). FIB-4 across all dose groups was 1.3. Median reduction in MRI-PDFF was 42% and 52% in the paired biopsy population at resmetirom 80mg and 100mg. Among patients treated with resmetirom 80mg or 100mg who

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164 | GLOBAL PREVALENCE OF INFECTIONS AND IMPACT OF REGIONAL VARIATIONS ON OUTCOMES: MULTI-NATIONAL CONSORTIUM OF CIRRHOSIS STUDY

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Background: Regional differences in environment, health-care system, microbiology lab capabilities, countermeasures of drug resistance may greatly impact the occurrence and evolution of infection in cirrhosis. We aimed to assess the prevalence, characteristics, clinical impact, and variations in infection on admission (AdI) across a global population of cirrhosis inpatients. **Methods:** CLEARED Consortium prospectively recruited inpts with cirrhosis from 6 continents. Data were collected at baseline and followed during admission. Infections diagnosed empirically or by culture using prespecified criteria within 48 hrs of admission were defined as AdI. Comparisons were made between pts w/wo AdI & between regions. Multivariable (MV) analysis for in-hospital mortality was performed using admission variables. **Results:** AdI was identified in 1351 pts (32%) among 4238 pts from 27 countries. Major site was SBP (28.9%), respiratory (RTI, 17.3%) & UTI (14.3%). No organism was isolated in 48%, then G- (25%), G+(11%) & fungal (3%). Among 580 AdI pts with isolated organisms, 20% had drug-resistant organisms (DRO). AdI vs No-AdI admission variables AdI and No-AdI pts had similar demographics and etiology of cirrhosis but ↑ MELD-Na (24 vs 19, $p < 0.001$), prior infections (33 vs 13%), ascites (69 vs 61%), overt HE (32 vs 24%), AKI (20 vs 14%) and transplant listing (11 vs 9%), all $p < 0.01$. AdI pts had ↑ use of lactulose (49 vs 39%), rifaximin (30 vs 21%), diuretics (57 vs 52%) and SBP Prophylaxis (16 vs 12%), all $p < 0.001$. AdI pts had ↑ HE (42 vs 32%), AKI (37 vs 17%), anasarca (43 vs 35%), & lower GI bleed (18 vs 28%) as causes of admission, all $p < 0.01$. Outcomes: AdI pts developed ↑ nosocomial infections (17 vs 11%), AKI (47 vs 28%), brain (19 vs 9%), respiratory (15 vs 6%) and circulatory failures (19 vs 7%), ICU transfers (25 vs 15%) and in-hospital (21 vs 7%), all $p < 0.001$. MV analysis identified AdI as a significant risk factor for in-hospital mortality (OR 2.78, $p < 0.0001$) independent of age (OR, 1.02, $p < 0.001$) baseline MELD-Na (OR 1.15, $p < 0.001$), prior GI bleed (OR 1.3 $p = 0.03$) and prior HCC (OR 2.00, $p = 0.002$), *etc*. Regional variations African sites

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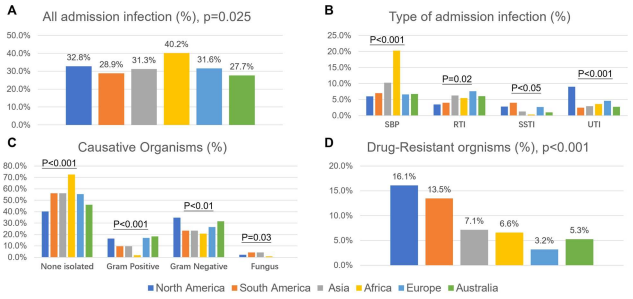
had the highest prevalence of AdI but lowest culture positivity (Fig A, C). SBP was highest in Africa while UTIs were highest in Nth Am (Fig B). RTI was higher in EU, Asia and Australia while skin and soft tissue infection was higher in Sth and Nth Am. The rest were similar. G- were higher in Nth Am & Australia while G+ were similar. Fungi were higher in Asia and America (Fig C). DRO varied across the continents and was influenced by insufficient culture positive isolates (Fig D). **Conclusion:** In this global cohort, one-third of the inpts with cirrhosis had AdI which increases risk of in-hospital mortality by ~3 fold. Tailored strategies should be developed for different regions due to the substantially different characteristics in terms of types, culture positivity rates, isolated causative organism(s) and DROs across regions.



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♦ 165 | AMONG YOUNG ADULTS SURVIVING A FIRST PRESENTATION OF ACUTE ALCOHOLIC HEPATITIS, FEMALES ARE AT 50% HIGHER RISK OF PROGRESSION TO CIRRHOSIS AND DECOMPENSATION

Jennifer A. Flemming, Queen's University, Maya Djerboua, Ices and Norah Terrault, University of Southern California, Los Angeles, CA

Background: Alcohol related harms to adolescents and young adults (AYAs) are on the rise and a priority group for identification and treatment to prevent progression of alcohol-associated liver disease

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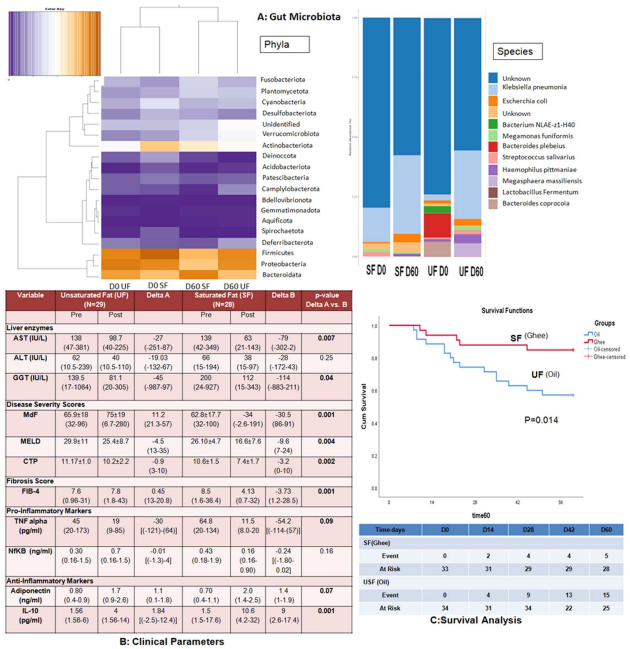

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169 | DECREASED MORTALITY IN PATIENTS WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS (SAH) TREATED WITH CORTICOSTEROIDS DURING THE COVID PANDEMIC

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Background: Corticosteroids are the standard of care for SAH in the absence of contraindications. Survival benefits conferred by steroids are often gained at the expense of increased infection risk. We investigated the co-incidental impact of infection mitigation measures during the COVID pandemic on mortality in SAH patients treated with corticosteroids. **Methods:** Data from 5 recent clinical studies were combined, 3 of which were conducted before the COVID outbreak, one during the pandemic, and one included a time-frame before and during the COVID. April 1, 2020 was defined as the start of COVID-19 outbreak period because the ongoing studies stopped recruitment in the early months of the pandemic. Mortality rates at 28, 90, and 180 days were compared between the pre and during-COVID pandemic periods in patients treated with corticosteroids. Cox regression analyses were performed to compare the survival while controlling for patient characteristics. **Results:** Data from 575 patients (415 from pre-COVID and 160 during COVID) were analyzed. Patients recruited during the COVID pandemic were slightly younger (43.7 vs. 46.5 in the pre-COVID period). Mean MELD scores were similar (25.7 for pre-and 24.8 for during-COVID periods). Mortality rates at 28 (11.6% vs 2.5%), 90 (22.4% vs 10%), and 180 (26.5% vs 15%) days were consistently higher for the pre-pandemic period (Figure 1A). Estimated survival probabilities were significantly higher during the pandemic (Figure 1B). After controlling for MELD and patient characteristics, the adjusted hazard ratios of the during-COVID period for 28, 90, and 180-days survival were 0.28 (95%CI [0.1,0.79]), 0.51 ([0.3,0.87]), and 0.57 ([0.36,0.89]), respectively (all $p < 0.05$). **Conclusion:** The markedly lower mortality rates in SAH patients treated with steroids after the COVID outbreak raise the possibility that infection mitigation measures enacted during the pandemic may have collaterally benefited patients on corticosteroid therapy.

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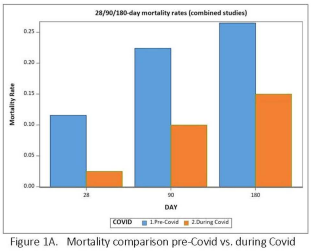

Figure 1A. Mortality comparison pre-Covid vs. during Covid

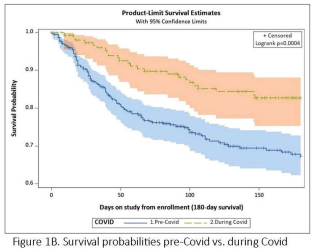

Figure 1B. Survival probabilities pre-Covid vs. during Covid

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170 | PRE-TREATMENT GUT MICROBIOTA PREDICTS SURVIVAL AFTER FECAL MICROBIOTA TRANSPLANTATION IN SEVERE ALCOHOLIC HEPATITIS

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Background: New therapeutic alternatives to corticosteroids in severe alcohol-associated hepatitis (SAH) is unmet need. Fecal microbiota transplantation (FMT) has been proposed as it targets well-established pathophysiological pathway but, data is scarce and many unanswered questions remain. One of the principal tools for personalized management of SAH is selection of patients whose potential to benefit from FMT is increased based on their pre-FMT gut-microbiome analysis. Aim: To search for patterns in the pre-FMT gut microbiome of patients with SAH which are associated with increased probability of response to FMT (survival). **Methods:** We enrolled 36 adult consenting patients with SAH and 20 healthy controls; fecal samples were collected at time of SAH diagnosis at HEGITO and from healthy controls at the Faculty of Chemical and Food Technology. After DNA isolation using QIAamp PowerFecal Pro DNA Kit (Qiagen), microbial profiling was performed using 16S ribosomal RNA amplicon sequencing. The libraries were prepared using the (PCR) products according to the MiSeq System guidelines (Illumina), obtained data were analyzed with QIIME 2. **Results:** Dysbalanced gut microbiota of SAH patients was typical for elevated levels of pathogens and opportunistic pathogens including Enterococcus, Eggerthella, Fusobacterium and decrease of beneficial bacteria like Faecalibacterium, Eubacterium, Coprococcus, Barnesiella and Roseburia. Antibiotic treatment of infections preceding FMT (ATB) affected microbiota community with significantly prevailing Enterococcus spp., hence compromising the informativeness of its composition. On the other hand, microbiome of patients without ATB was enriched in Streptococcus sp., Actinomyces sp. or Escherichia/Shigella sp., ($p < 0.05$), and we were able to determine a predictive potential of gut microbiome for survival after FMT. Survivors possessed higher relative abundance of short-chain-fatty acids (SCFA) producers Faecalibacterium, Subdligranulum or unspecified Ruminococcaceae. **Conclusion:** Pre-FMT abundance of certain SCFA producing taxa is associated with better survival after FMT for SAH which might prove to be of predictive and therapeutic potential, respectively; ATB for infections erase predictive potential.

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ammonia (AUROC 0.81, 95% CI 0.71-0.91). In multiple logistic regression analysis, CL-ART remained an independent predictor of future HE admissions (OR 1.15, $p = 0.049$). Using the Youden index, the optimal CL-ART cut-off to predict HE-related admissions is 26s (sensitivity 91.7%, specificity 71.4%). When analysing all subsequent admissions due to any decompensation event, baseline CL-ART scores were significantly higher in those subsequently hospitalised (27.0 vs 21.3s, $p < 0.001$) with an AUROC of 0.76 (95% CI 0.66-0.85). Finally, the CL-ART also demonstrated superior participant useability (Figure 1). **Conclusion:** This study demonstrates that CL-ART can help predict hospitalisation due to all decompensation, with highest sensitivity and specificity for HE-related admissions. Its rapid testing, smartphone application and high useability mean it can be used remotely, and therefore, play a crucial role in predicting decompensation, enabling early community intervention.

Test Question	PHES	EncephalApp	CL-ART
The test is easy to perform (1-10)	7.32	8.08	9.17
The test seems an appropriate length of time (1-10)	7.91	8.17	9.24
I would feel comfortable doing this test again (1-10)	8.26	8.60	9.34

Figure 1: Sample smartphone display of a CL-ART test question and the mean results from participant feedback questionnaires. A scale of 1-10 was used, where 1 represented 'completely disagree' and 10 represented 'completely agree'.

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216 | LINKAGE OF LIVER STIFFNESS WITH COGNITIVE PERFORMANCE ACROSS THE SPECTRUM OF CHRONIC LIVER DISEASE AND IMPACT ON QOL: A MULTI-NATIONAL STUDY

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Background: Quality of life and symptom management are important for patients with chronic liver disease (CLD), which can precede cirrhosis development. CLD patients with/without cirrhosis have mood disorders which affect cognition. Cognitive impairment is testing using simple (Animal naming, ANT) or more complicated [Stroop and Psychometric hepatic encephalopathy score (PHES)] but their impact on QOL across the spectrum of CLD is unclear. Aim: Evaluate determinants of poor QOL across the CLD spectrum in a multi-center study. **Methods:** Outpatients with compensated cirrhosis and with pre-cirrhotic liver disease (F1-F3) were enrolled prospectively in 2 centers. Demographics, disease etiology, and co-morbid conditions were recorded. Fibroscan was performed. We evaluated depression & anxiety (Beck inventories BDI/BAI), PTSD, medications (psychoactive, PPI, diabetes), and alcohol use (AUDIT) and performed cognitive testing using ANT, PHES, and EncephalApp Stroop (has Off and OnTimes). Finally, the Sickness Impact Profile (SIP, generic QOL instrument with psychosocial and cognitive domains) was administered. Comparisons of those with/without cirrhosis were performed and Fibroscan kPa were correlated with cognition & QOL. Linear regression for prediction of physical & psychosocial SIP was performed for all pts using cirrhosis/not as a covariate. **Results:** We included 116 outpatients (11 F2, 34 F3 and 72 F4) from USA & Denmark. As shown in table 1, pts with cirrhosis were older, more likely to have alcohol, and lower likelihood of NAFLD (FigA). Other demographic measures, BMI, & co-morbid conditions/medications were similar. Cirrhosis pts as expected had higher Fibroscan kPa & creatinine/bilirubin. PROs: Beck inventories were worse in non-cirrhotic patients while frailty & alcohol intake were similar. QOL: SIP was higher (worse) in patients without cirrhosis, especially related to physical score. Cognitive testing: EncephalApp Off Time was higher in cirrhosis while other tests were statistically similar. Correlation with Fibroscan: EncephalApp OffTime ($r = 0.4$, $p < 0.0001$) and PHES Score ($r = -0.4$, $p = 0.003$) were linked with kPa (Fig B/C). No correlation of kPa with SIP was seen. Regression: *SIP physical*: higher BDI (T-value 2.32, $p = 0.02$), EncephalApp Offtime (2.80 $p = 0.006$) and lower age (-2.59, $p = 0.01$) were linked. *SIP psychosocial*: BDI (2.88, $p = 0.005$) & EncephalApp Offtime (2.25, $p = 0.03$) and BAI (4.09, $p < 0.0001$) were linked. Cirrhosis status was not significant. **Conclusion:** In a multi-center cohort of outpatients across the spectrum of CLD from F2 through compensated cirrhosis, we found that QOL was worse in pre-cirrhotic vs cirrhosis stages. Liver stiffness was linked with cognition, while QOL was correlated with mood disorders, which were higher in pre-cirrhotic stages. Mood disorders and impaired cognitive performance are independent determinants of QOL in a

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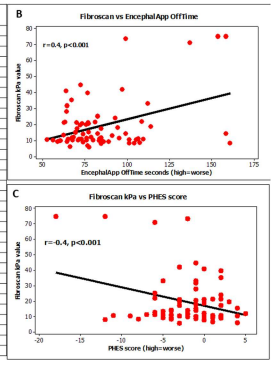
wider spectrum of CLD and should be elicited in all patients.

A: Comparison of QOL, Cognitive, Clinical and Mood parameters	No-cirrhosis (n=44)	Cirrhosis (n=72)	P value
Age (years)	**49.9±14.4**	**60.3±11.4**	**<0.001**
Male sex	25	34	0.32
Non-White	5	15	0.18
Education (years)	12.2±3.2	11.9±2.9	0.56
Comorbidities			
Diabetes	9	22	0.21
On PPI	14	16	0.26
On psychoactive meds	28	52	0.33
On opioids	4	3	0.29
On statins	13	18	0.59
On CV medications			
Beck depression inventory (↑=worse)	**12.0±10.3**	**6.3±6.8**	**0.002**
Beck Anxiety inventory (↑=worse)	**9.4±9.1**	**6.2±6.2**	**0.04**
Clinical frailty scale (0-9)	1.4±0.9	1.7±1.1	0.24
AUDIT-C (↑=worse)	4.1±5.8	3.2±4.1	0.41
BMI (kg/m2)	34.6±8.4	33.0±7.8	0.33
Cirrhosis details			
Alcohol etiology	**4**	**19**	**0.02**
NASH etiology	**28**	**28**	**0.009**
kPa (Fibroscan)	**10.0±2.5**	**25.1±17.8**	**<0.001**
INR	1.0±0.3	1.1±0.2	0.31
Bilirubin (mg/dl)	0.7±0.6	0.9±0.9	0.07
Creatinine (mg/dl)	**0.8±0.2**	**0.9±0.5**	**0.05**
Cognitive testing			
Mini-mental status (out of 30)	29.4±1.1	29.4±1.0	0.86
Animal naming (↑=better)	21.6±6.9	20.0±6.9	0.22
PHES (↑=better)	-1.40±3.99	-1.87±3.81	0.54
EncephalApp OffTime (↑=worse)	**73.5±15.1**	**84.3±27.1**	**0.008**
EncephalApp OnTime (↑=worse)	88.2±21.3	94.8±27.1	0.16
SIP (high=worse QOL)			
Psychosocial score (↑=worse)	10.4±12.5	6.5±9.3	0.07
Physical score (↑=worse)	**8.3±8.5**	**4.9±7.7**	**0.04**



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217 | EFFICACY OF VITAMIN C ON AKI OUTCOMES IN CRITICALLY ILL PATIENTS WITH CIRRHOSIS AND MULTIDRUG-RESISTANT BACTERIAL INFECTIONS- A RANDOMIZED CONTROLLED TRIAL [NCT04494451

Rakhi Maiwall[1], Ashinikumar Kumar Hidam[2], Neha Chauhan[2], Samba Siva Rao Pasupuleti[3], Vikas Khillan[2], Harsh Vardhan Tevethia[1], Rajan Vijayaraghavan[2], Anupam Kumar[2], Sherin Thomas[2] and Shiv Kumar Sarin[4], (1)Institute of Liver and Biliary Sciences, New Delhi, (2)Institute of Liver and Biliary Sciences, (3)Mizoram University (A Central University), Pachhunga University College Campus, (4)Ilbs

Background: Infections with multidrug-resistant organisms (MDR) are a common cause of organ failures and increased fatality in patients with cirrhosis. Sepsis is associated with increased oxidative stress with widespread endothelial, cellular injury and acute deficiency of vitamin C. Polymyxins used for MDR infections have increased incidence of nephrotoxicity. We aimed to evaluate the impact of vitamin C on outcomes of sepsis-associated acute kidney injury (SA-AKI). **Methods:** Patients with nosocomial acquisition or proven MDR infections underwent open-label randomization into two groups. Group 1-received iv vitamin C (25 mg/kg or 1.5 gram maximum every 6 hourly) for 5 days along with polymyxin antibiotics while group 2 (SMT) received iv antibiotics alone. Primary end-point was AKI progression at day 5. Intention-to-treat analysis was performed. In a subset of patients ($n = 20$), we performed ELISA of plasma levels of vitamin-c, syndecan-1- a marker of endothelial glycocalyx degradation, von willebrand factor (vWF), and ADAMTS13 (a disintegrin and metalloproteinase thrombospondin motif) as markers of endothelial injury and microcirculation. **Results:** A total of 100 patients, 50 in each group, with mean age 48.7 ± 9.8 years, lactate 2.67 ± 2.27 μmol/L, SOFA scores 11.1 ± 3.6, 91% males, 60% alcohol-related were randomized. The KDIGO stage at enrolment was comparable 1:2:3 (68%:14%:18% vs. 64%:16%:20%; $p = 0.91$). Pneumonia was the commonest infection in 61%. Culture-proven MDR infections were seen in 51% patients, commonest being Acinetobacter baumannii (45.1%) and Klebsiella pneumoniae (27.4%). On intention-to-treat analysis, at day 5, AKI progression was significantly lower in Vit-C+SMT (18% vs. 54%; $p < 0.001$) with higher reversal of shock (56% vs. 22%; $p = 0.001$), lactate clearance at 12 hrs. (60% vs. 32%; $p = 0.009$) and 24 hrs. (56% vs. 34%; $p = 0.044$), reduction in SOFA score at 48 hrs. (52% vs. 26%; $p = 0.013$), and higher AKI recovery at day 14 compared to SMT (61.2% vs. 32%; $p < 0.001$) respectively. The 28-day mortality, need of dialysis, duration of ICU stay and mechanical ventilation were not different. There were no major adverse events requiring Vitamin C discontinuation, 20% patients developed thrombocytopenia. At day 5, a significant reduction in ADAMTS13, syndecan-1 and elevation in vWF levels and Vitamin-c levels were observed in Vit-C+SMT vs. SMT group.(Figure) **Conclusion:** Vitamin C improves outcomes of SA-AKI in cirrhosis patients with MDR infections. Reduction in endothelial injury, stabilization of endothelial glycocalyx with improvement in microcirculation, and possible reduction in nephrotoxicity of polymyxin antibiotics could be potential mechanisms of the observed benefit.

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238 | IMPACT OF BMI ON NIS2+TM AND ESTABLISHED NON-INVASIVE TESTS FOR THE EVALUATION OF NON-ALCOHOLIC LIVER DISEASE

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Background: While obesity is a risk factor for NAFLD, patients across the BMI spectrum are affected by the disease, creating a need for reliable non-invasive tests (NITs) with performances that are not affected by BMI. While most of standard NITs are designed to detect advanced fibrosis, NIS2+™, an optimization of the blood-based NIS4® technology, is specifically designed to detect at-risk NASH (NAS $\geq$ 4; F $\geq$ 2). We aimed to isolate the effect of BMI on NITs and assess their clinical reliability across the BMI spectrum. **Methods:** Among all non-cirrhotic NASH patients enrolled in the RESOLVE-IT Phase 3 trial (NCT02704403), those with data for NIS2+™, APRI, NFS, FIB-4, ELF™ and FibroScan (FS) were selected (n = 898). This cohort was split in 4 BMI-based subgroups: non-obese, Class 1, 2 and 3 obesity. To isolate the effect of BMI from confounding factors, we matched the 4 groups for the histology and other comorbidities using a propensity score matching algorithm, resulting in 4 groups of n = 113 patients. One-way ANOVA tests were used to evaluate the BMI impact on NITs and biomarkers distribution. Impact on clinical performances (sensitivity, specificity) was also analyzed using fixed cutoffs. **Results:** NFS was impacted by BMI ($p < 0.0001$), with scores increasing along with BMI. The significant decrease in albumin concentration with BMI ($p < 0.0001$) and the presence of BMI in the NFS equation explain the NFS results. FS distribution was significantly impacted by BMI ($p < 0.0001$), displaying increased mean scores in Class 3 obesity compared to other groups (14.3 kPa vs 10.1-11.0kPa). The BMI impact on NFS and FS distributions resulted in a decrease in specificity with increasing BMI when ruling-out (NFS: 76% to 20%; FS: 49% to 33%) and ruling-in (NFS:100% to 83%; FS 76% to 48%) F $\geq$ 3. While NFS sensitivity progressively increased with BMI when ruling-out (NFS: 52% to 90%) and ruling-in (NFS:2% to 33%) F $\geq$ 3, FS achieved the highest sensitivity in class 3 obese patients compared to other groups (rule-out: 94% vs 76-88%; rule-in: 82% vs 60-68%). NIS2

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+TM, APRI, ELFTM and FIB-4 were not significantly impacted by BMI, resulting in stable clinical performance. **Conclusion:** NIS2+TM, FIB-4, APRI and ELFTM were not significantly impacted by BMI. NFS was, however, significantly impacted by BMI, notably due to BMI-associated differences in albumin levels. Liver stiffness by FS was also significantly impacted in Class 3 obesity. This suggests a need for BMI-adapted cutoffs for these particular NITs.

Table: NITs scores and associated biomarkers means evolution across BMI matched-groups

	Non-obese (n=113) (18.5≤BMI<25)***	Class 1 Obesity (n=113) (25≤BMI<30)***	Class 2 Obesity (n=113) (30≤BMI<35)***	Class3 Obesity (n=113) (BMI≥35)***	p value
NIS2+TM*					
NIS2+TM **	0.72±0.22	0.67±0.23	0.71±0.2	0.68±0.22	0.1766
miR34-a (FoldC)*	1.83±1.93	1.34±1.14	1.55±1.5	1.52±2.2	0.1439
YKL-40 (ng/mL)*	107±174.66	77.28±59.11	92.03±82.22	88.76±71.38	0.4396
FIB-4/NFS/APRI					
FIB-4*	1.5±1.16	1.39±0.86	1.34±0.64	1.35±0.76	0.8482
NFS	-2.03±1.42	-1.54±1.28	-1±1.33	-0.18±3.22	<0.0001
APRI*	0.71±0.61	0.66±0.49	0.64±0.5	0.6±0.39	0.8211
Ast (IU/L)*	33.3±38.1	49.69±29.79	49.35±34.1	47.88±27.45	0.6039
Alt (IU/L)*	75.47±54.54	74.89±51.14	71.35±51.17	66.5±43.44	0.476
Platelet (10e9/L)	245.79±71.43	235.68±64.07	238.41±67.93	238.65±60.71	0.7251
FPG (mmol/L)*	6.48±2.4	5.92±1.63	6.4±1.98	6.46±1.89	0.0578
Albumin (g/L)	46.55±3.15	46.42±2.52	45.09±2.71	43.97±2.83	<0.0001
ELFTM*					
ELFTM	9.62±1.01	9.51±0.84	9.61±0.87	9.66±1.04	0.656
Hyaluronic acid (ng/mL)*	78.45±86.11	64.11±60.69	65.76±54.26	77.58±110.76	0.901
PINP (ng/mL)*	11.9±5.97	11.41±5.1	12.16±5.27	12.9±6.27	0.1679
TIMP1 (ng/mL)*	276.77±68.32	262.39±65.26	273.79±60.6	293.54±80.96	0.0123
FibroScan					
FibroScan*	10.32±7.89	10.14±4.37	10.96±5.76	14.29±9.88	<0.0001
Other Biomarkers					
Ast/Alt ratio*	0.81±0.36	0.72±0.25	0.73±0.19	0.8±0.31	0.09
GGT (IU/L)*	99.7±161.99	89.07±110.28	60.56±46.16	86.74±102.35	0.0638
Triglycerides (mmol/L)*	2.63±4.13	2.3±1.65	2.34±2.19	2.05±1.11	0.7095
Total cholesterol (mmol/L)	5.17±1.4	4.94±1.13	4.75±1.13	4.81±1.18	0.0796

[a] p values have been computed using Chi² tests for proportion comparisons and Welch-adapted one way ANOVA tests for numerical features.
[b] * indicates variables that have been log10-transformed for p values computation. ** indicates variable that has been logit-transformed for p values computation.
[c] *** BMI (kg/m²) categories adapted for Asian people: Non-obese (18.5≤BMI<25), Class 1 Obesity (25≤BMI<30), Class 2 Obesity (30≤BMI<35) and Class 3 Obesity (BMI≥35).

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239 | CLINICAL, BIOLOGICAL AND IMAGING PREDICTORS OF AT-RISK METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH): COMBINED DATA FROM MULTIPLE THERAPEUTIC TRIALS INCLUDING MORE THAN 6,000 PATIENTS (IN COLLABORATION WITH NAIL-NIT CONSORTIUM)

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Background: The identification of at-risk metabolic dysfunction-associated steatohepatitis (MASH) patients remains a main challenge in both clinical practice and clinical trial settings. Several non-invasive biomarkers have been developed to identify those at-risk MASH patients who would benefit from pharmacological therapy. We aimed to describe the main predictors of at-risk MASH across multiple therapeutic clinical trials. **Methods:** We combined screening data from 7 MASH non-cirrhotic phase 2 trials. Predictors of at risk-MASH were examined using logistic regression and excluding patients with cirrhosis **Results:** Out of the 6,558 patients, 2,173 with centrally assessed liver biopsy were included. Among them, 912 (42%) met the histopathological criteria for at-risk MASH. The predictors of at-risk MASH are shown in Table 1. The proportion of at risk-MASH patients was 12%, 26%, 42% and 61% in patients with AST < 20, AST 20-30, AST 30-40, and AST ≥ 40, respectively. This rises to 54% in patients with AST ≥ 30 versus 23% in patients with AST < 30. In patients with FAST < 0.35, FAST 0.35-0.67, and FAST ≥ 0.67, 34%, 58%, and 74% were "at-risk MASH", respectively. This rises to 69% for patients with FAST ≥ 0.5 versus 40% in patients with FAST < 0.5. When focusing on Fib-4 categories (< 1.3, 1.3-

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	DSA level				
AMR positive / total patients	High	Intermediate	Low	No Risk	Total
AMR risk level by Crossmatching: High	2 / 20	0 / 2	0 / 1	0 / 0	2 / 23
Intermediate	1 / 17	0 / 11	1 / 9	0 / 0	2 / 37
Low	0 / 0	0 / 2	0 / 6	0 / 1	0 / 9
No Risk	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
Total	3 / 37	0 / 15	1 / 16	0 / 1	4 / 69

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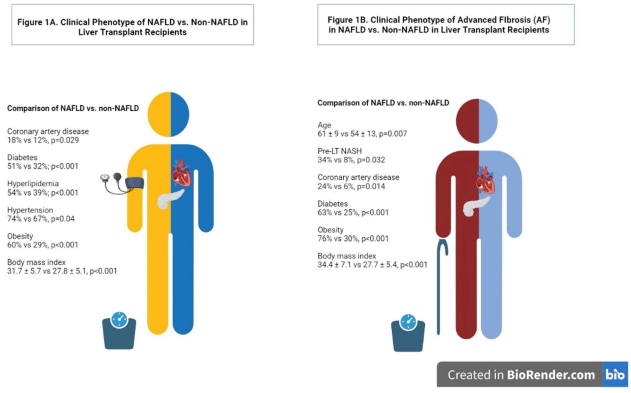
1070-A | EFFECTIVE USE OF VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY TO IDENTIFY DISTINCT CLINICAL PHENOTYPES OF LIVER TRANSPLANT RECIPIENTS WITH ADVANCED FIBROSIS AND NON-ALCOHOLIC FATTY LIVER DISEASE

Dempsey L Hughes[1], Mauricio Garcia Saenz de Sicilia[2], Andres Duarte-Rojo[3], Tamoore Arshad[4], Katie M Rude[2], Lyle Burdine[2], Richard T Spencer-Cole[2] and Mohammad S. Siddiqui[4], (1)Northwestern University, (2)University of Arkansas, (3)Northwestern University Feinberg Scho, (4)Virginia Commonwealth University

Background: Occurrence of nonalcoholic fatty liver disease (NAFLD) after liver transplantation (LT) is becoming increasingly common. While pre-LT NAFLD is associated with metabolic syndrome, the clinical phenotype of NAFLD and advanced fibrosis in LT recipients is not as well defined despite exposure to chronic immunosuppression placing these patients at higher metabolic risk. Vibration-controlled transient elastography (VCTE) has emerged as an effective, non-invasive method to determine presence of graft steatosis and fibrosis. We sought to determine if VCTE could distinguish clinical phenotypes of LT recipients with graft NAFLD and, moreover, compare NAFLD patients with advanced fibrosis (AF) to non-NAFLD patients with AF. **Methods:** LT recipients at two major LT centers underwent standard of care, fasting vibration controlled transient elastography (VCTE) between January 2015 and January 2022. Only patients with successful VCTE (10 valid readings with IQR/Median < 30%) were included. Patients with risk factors for inaccurate liver stiffness measurement (concurrent heart failure, hemodialysis-dependence, cholestatic hepatitis, chronic rejection) were excluded. Per previously established VCTE cut-off values, post-LT NAFLD was defined as CAP > 270 dB/m and advanced fibrosis was defined as > 10.5 kPa. **Results:** A total of 547 LT recipients completed VCTE. The median time from LT to VCTE was 28 months. NAFLD was present in 234 patients (43%), and advanced fibrosis was present in 94 patients (17%). The most common etiology of cirrhosis in the post-LT NAFLD group was NASH (32%) compared to alcohol (30%) in the non-NAFLD group. The overall burden of metabolic co-morbidities was significantly high and was even higher among patients with post-LT NAFLD (Figure 1A). No significant biochemical differences in NAFLD vs. non-NAFLD were noted except for higher triglycerides in the NAFLD group (189 ± 144 vs 132 ± 68, $p < 0.001$). The prevalence of metabolic comorbidities such as coronary artery disease, diabetes and obesity increased even further among patients with NAFLD and AF when compared to non-NAFLD AF (Figure 1B). **Conclusion:** VCTE is capable of identifying distinct clinical phenotypes of LT recipients with NAFLD and advanced fibrosis, and the present study provides novel data linking occurrence of post-LT NAFLD to higher metabolic disease burden. Moreover, progression to advanced hepatic fibrosis leads to further deterioration in metabolic health. These clinical phenotypes (Figure 1) should allow for better risk stratification and mitigation strategies in LT recipients to optimize outcomes. Further study is needed to confirm impact of at-risk clinical phenotypes on post-LT graft and patient outcomes. Mechanistic studies are also required to better understand the development of these distinct clinical phenotypes despite similar immunosuppression exposure.



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1071-A | END-OF-LIFE CARE FOR PATIENTS WITH END-STAGE LIVER DISEASE REMOVED FROM THE LIVER TRANSPLANT WAIT LIST

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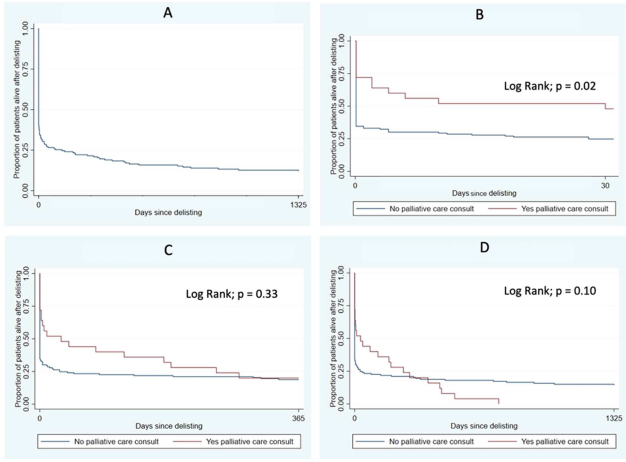
Background: Patients with end-stage liver disease (ESLD) who are not candidates for liver transplantation (LT) are at high risk of short-term mortality and infrequent or late involvement of palliative care (PC). The aim of this study is to characterize end-of-life care for patients removed from the LT waitlist. **Methods:** We performed a retrospective review of patients at our institution who had been listed for LT and removed from the waitlist because of medical or psychosocial contraindications between 2017 and 2022. **Results:** A total of 158 patients were included, with 19 patients alive at the end of the study period. The mean age was 57.3 ± 10.4 years with most patients being male (66%), White (91%), and having alcohol-related liver disease (53%). The mean biologic Model for End Stage Liver Disease-Sodium when patients were listed for LT was 17.8 ± 8.9, compared to 26.8 ± 11.7 at delisting ($p < 0.001$). The most common reason for delisting was sepsis (45%). Of the patients who died, 73% died in the hospital, 18% with hospice, 9% at home without services, and 1% at a skilled rehabilitation facility. Of the study patients, 70% were admitted to the intensive care unit during their terminal hospitalization or after delisting, with 49% mechanically ventilated, 47% having an enteral access device placed, and 41% being initiated on renal replacement therapy. A PC consult was performed for only 16% of patients, primarily when patients were hospitalized. The mean days from delisting to death was 147.4 ± 205.7 for patients with a PC consult and 59.6 ± 205.7 for patients without a PC consult. Patients with a PC consult had a statistically significant survival benefit up to 1 month ($p = 0.02$), but statistical significance did not persist over the entire study period ($p = 0.10$) (Figure 1A-D). Out of the 101 patients who died in the hospital, 93% were delisted and died on the same day and 89% were delisted and died during the same hospitalization. **Conclusion:** Patients with ESLD who are ultimately removed from the LT wait list are frequently delisted right before death, often in the setting of septic shock and intensive medical interventions without PC involvement. This likely reflects a culture of PC interventions starting when disease directed therapy ends and may delay recognition of when a patient is irreversibly too sick for transplant. This study will inform our future work to explore which patients on the LT wait list who are admitted to the hospital are at high risk of delisting and death and may benefit from early PC consultation. Figure 1A-D. Kaplan-Meier estimates demonstrating survival of study patients. Panel A reflects overall study survival for the entire study cohort during the study period. Panels B-D demonstrate survival for patients with or without a palliative care consultation at 30 days (B), 365 days (C), and at the end of the study period (D).



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1072-A | EVALUATION OF THE EFFECT OF THE COVID-19 PANDEMIC ON THE RATE OF CLOSTRIDIUM DIFFICILE INFECTION FOLLOWING LIVER TRANSPLANTATION

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was statistically lower than NHWs. Once listed, the percentage of AIs undergoing LT was similar to NHWs. Alcohol (ALD) and NASH cirrhosis comprised 64% of LT indications for AI patients. ALD prevalence increased from < 20% in 2017 to 37.5-100% in subsequent years. No cholestatic or autoimmune ESLD was observed. The AI cohort had 9 (33.3%) graft failures and 7 (25%) deaths. Total graft failures and deaths were significantly higher in AIs than NHWs. Causes of graft failure or death included: primary non-function, DCD-cholangiopathy, metastatic hepatobiliary malignancy, chronic rejection, COVID-19, acute-on-chronic respiratory failure, hemorrhagic stroke, and cardiac arrest. **Conclusion:** AIs comprised a small percentage of those referred for LT at a large LT center positioned in a favorable geographic area to serve AI patients. This was higher than the overall UNOS percentage but likely lower than expected for the geographic area. Of AIs referred for LT, a substantially smaller percentage were transplanted despite the same leading indications for LT. In our cohort, the lower number referred that were transplanted and lower number evaluated that were waitlisted accounted for the disparity. Graft and patient survival were also significantly lower. We suspect these disparities are attributable to social determinants of health such as language barriers, transportation, and unfamiliarity with the transplant process. Novel interventions such as an AI patient navigator are needed to achieve health equity.

Table 1.

Patient Volumes	Native American	African American	Hispanic Latino	Non-Hispanic White	Center Total	p
Referrals	135	46	621	1751	3218	N/A
Evaluations	80	37	485	1349	2092	N/A
Wait List Additions	29	21	285	838	1229	N/A
Liver Transplants	27	20	206	720	1051	N/A
Comparison of Native American and Non-Hispanic White Experiences						
Percent of referred evaluated	59	80	78	77	65	0.071
Percent of evaluated added to wait list	36	57	58	62	59	0.014*
Percent of wait listed transplanted	93	95	72	86	86	0.768
Percent of referred transplanted	20	43	33	41	33	0.001*
Percent evaluated transplanted	34	54	42	53	50	0.001*
Comparison of Graft Outcomes of Native American and Non-Hispanic White Transplants n (%)						
Total graft failures	9 (33)	3 (15)	33 (16)	99 (14)	144 (14)	0.001*
Graft failures within 1 year	4 (15)	2 (10)	23 (11)	55 (8)	86 (8)	0.076
Deaths	7 (26)	3 (15)	23 (11)	61 (8)	96 (9)	0.008*
Deaths within 1 year	3 (11)	2 (10)	14 (7)	27 (4)	48 (5)	0.075

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1122-A | THE RELATIONSHIP BETWEEN SERUM ATHEROGENIC RISK AND NONALCOHOLIC FATTY LIVER DISEASE AMONG LIVER TRANSPLANT RECIPIENTS

Shreya Garg[1], Alok Baral[1], Audrey Ang[1], Madison Nguyen[1], Rehan Razzaq[1], Tamoore Arshad[1], Hiba Khan[1], Ian O'Connor[1], Siddiq Elmahdi[1], Michael Tseng[1], Vaishali Patel[1], Margery Connelly[2] and Mohammad S. Siddiqui[1], (1)Virginia Commonwealth University Health System, (2)University of Florida

Background: Liver transplant (LT) recipients are at increased risk of atherosclerotic cardiovascular disease. A strong association between nonalcoholic fatty liver disease (NAFLD), fibrosis severity and atherosclerosis has been demonstrated in the general (e.g. non-transplant) population, however, no such data exists in LT recipients. Thus, it remains unclear if the presence of NAFLD increases the risk of atherosclerosis above and beyond that of LT alone. Thus, the aim of the current study was to better define the interaction between atherosclerosis and NAFLD among LT recipients. **Methods:** In this prospective study, 111 LT recipients were prospectively enrolled. All study participants underwent vibration controlled transient elastography and had blood drawn after an overnight fast. A controlled attenuation parameter (CAP) value > 270 dB/m was defined as presence of NAFLD. Atherogenic risk was quantified via NMR-based measurement of LDL, VLDL and HDL particles. Lipoproteins associated with increased atherogenic risk include smaller LDL and HDL size and increased small LDL and large VLDL particle concentrations with a concomitant decrease in large HDL particles. **Results:** Prevalence of NAFLD was 52% in the LT recipient cohort. Plasma LDL-C was similar between patients with and without NAFLD, however, patients with NAFLD had lower HDL-C (44 ± 16 vs. 56 ± 16 mg/dL; $p < 0.001$) and higher triglycerides (185 ± 121 vs 122 ± 51 mg/dL; $p = 0.003$). LT recipients with NAFLD had a more atherogenic lipoprotein profile characterized by smaller LDL particle size (20.54 ± 0.67 vs. 20.94 ± 0.53 nm; $p = 0.019$), HDL particle size (8.99 ± 0.51 vs. 9.37 ± 0.64 nm; $p < 0.001$) and VLDL particle size (50.4 ± 9.0 vs 45.1 ± 8.0 nm; $p < 0.001$). NAFLD was associated with an increase in size and concentration of atherogenic VLDL and LDL particles, and a decrease in anti-atherogenic HDL particles (Figure 1). Finally, Lipoprotein Insulin Resistance Index (LP-IR), a composite measure of atherogenic lipoprotein concentrations and insulin resistance that is linked to increased CVD risk, was significantly higher among LT recipients with NAFLD (56 ± 22 vs $37 \pm 20\%$; $p < 0.001$). **Conclusion:** The presence of NAFLD in LT recipients is associated with increased

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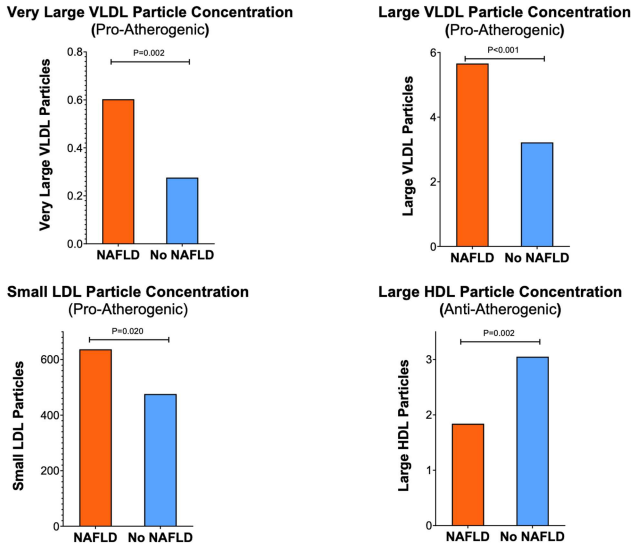
markers of atherosclerotic risk and thus establishes post-LT NAFLD as a risk factor for CVD. Additional prospective studies are required to better understand how NAFLD and circulating lipoproteins may interact together to promote atherosclerotic events.

FIGURE 1: Impact of NAFLD on Lipoproteins in LT recipients



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Disclosure information not available at the time of publication: Madison Nguyen, Rehan Razzaq, Tamoore Arshad, Ian O'Connor, Siddiq Elmahdi, Michael Tseng

1123-A | THE ROLE OF IMMUNOSUPPRESSION REGIMEN CHOICE ON THE RISK OF EARLY AND LATE OPPORTUNISTIC INFECTIONS AFTER LIVER TRANSPLANTATION

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Background: The burden of opportunistic infections (OIs) after liver transplantation (LT) has not been evaluated on a large scale. Further, the significance of certain clinical factors, such as immunosuppression decision-making, on this risk in adults is unknown. **Methods:** This was a retrospective cohort study of first LT alone recipients between 1/1/2007-12/31/2016 using Medicare claims data linked to the Organ Procurement and Transplantation Network database. Early ($\leq$1 y from LT) and late ($>$1 y) hospitalizations for OIs were identified using validated ICD-9/10 codes. Multivariable Cox proportional hazards models evaluated the factors independently associated with early or late OI hospitalization. Patients were censored at death, retransplantation or end of follow-up. **Results:** The study cohort (n = 11,320) was 64.0% male, 71.9% White, 14.7% Hispanic, and 8.1% Black with median age of 61 years (IQR: 54-66). Liver disease etiologies included: hepatitis C virus (36.3%), alcohol-associated liver disease (ALD; 21.7%) and non-alcoholic steatohepatitis (NASH; 14.5%). Median follow-up time was 4.7 years (IQR: 2.8-7.1). During follow-up, 13.2% of the cohort had $\geq$1 OI hospitalization. Among the 2,638 individual OI hospitalizations identified, 61.9% occurred $\leq$1 year from LT. OI causes included: cytomegalovirus (45.4%), aspergillus and endemic mycoses (20.6%), disseminated candidiasis (10.8%), varicella zoster virus (12.7%), tuberculosis and non-tuberculous mycobacteria (4.4%) and other (4.2%). Neither induction therapy ($p = 0.173$) nor maintenance regimen at LT discharge ($p = 0.288$) were associated with early OI hospitalization (Table). However, maintenance regimen at 1 year was associated with late OI hospitalization ($p < 0.001$) with steroid-based and mechanistic target of rapamycin inhibitor-based regimens conferring the highest risk (Table). An increased risk of early OI was also observed with NASH or primary sclerosing cholangitis (PSC; HRs 1.30 and 1.91 vs ALD; $p = 0.001$) and worsening creatinine (HR 1.11 per 1mg/dL; $p = 0.001$, and of late OI with PSC (HR 1.82 vs ALD; $p = 0.003$) and in women (HR 1.30; $p = 0.002$). **Conclusion:** Over 1 in 10 patients are hospitalized for an OI post-LT. While early immunosuppression choice was not associated with OI hospitalization $\leq$1 year from LT, maintenance regimen at 1 year led to a differential risk of late OI. Further evaluation of the increased risk of post-LT OI observed among female, NASH and PSC recipients is warranted.

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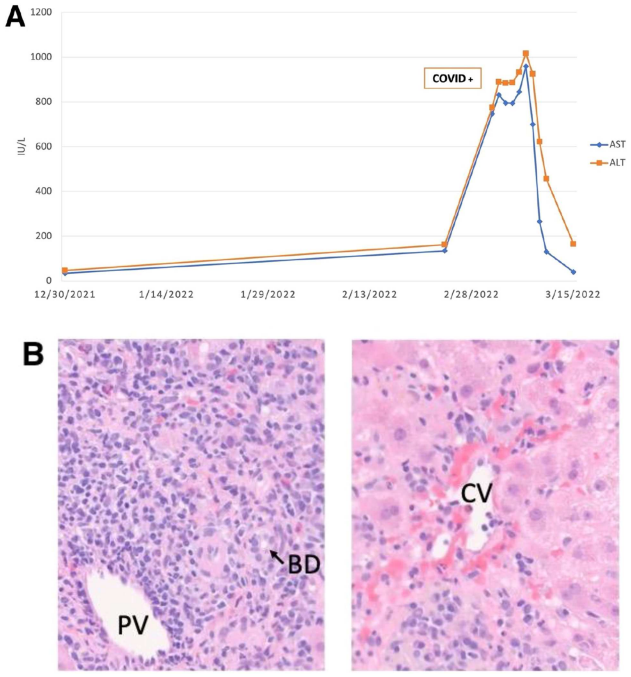
challenges given the chronic immunosuppression associated with transplantation. So far, studies have shown that immunosuppression itself does not seem to confer an increased risk of severe COVID disease and mortality in LT recipients. It is currently unclear whether the immune dysregulation associated with COVID-19 infection and/or modifications in immunosuppression increase the risk of rejection. **Methods:** Here we report a rare case of acute cellular rejection (ACR) following the onset of COVID-19 infection. The patient is a 59-year-old male with prior history of hepatitis C and alcoholic cirrhosis who had undergone deceased donor liver transplant 7 years prior. He was transitioned to tacrolimus monotherapy four months post-transplant and had stable graft function. Hepatitis C was treated post-transplant with successful sustained virologic response. **Results:** He presented with respiratory symptoms, with no recent travels or new medications prior. A respiratory viral panel was negative except COVID-19 PCR was positive. He was vaccinated with two doses of Pfizer-BioNTech a year ago. Liver enzymes were found to be significantly elevated on presentation from normal prior 2 months ago: ALT 775, AST 747, ALP 134, Tbili 1.6, tacrolimus level 9.1, Cr 1.2 (at baseline). Liver enzymes continued to progressively rise with peak levels ALT 1017, AST 959, AP 147, T Bili 2.1 (Fig 1 A). Serology was negative for acute viral infections (Hepatitis A, B, C, E, Epstein-Barr Virus and Cytomegalovirus). Alcohol levels on admission and phosphatidylethanol were negative. Liver ultrasound with doppler revealed patent hepatic vasculature and graft without intrahepatic or extra hepatic biliary dilation. Subsequent liver biopsy showed severe cellular rejection (Fig 1 B). The patient was treated with bolus methylprednisolone and increased tacrolimus goal 8-10. His liver enzymes subsequently improved and normalized entirely 2 months after the infection. **Conclusion:** To the best of our knowledge, this is one of the first reported cases of late ACR following COVID-19 infection. Prior studies have only reported ACR in the setting of withdrawing or decreasing immunosuppression in patients with COVID-19. In this case, the patient had maintained adequate level of immunosuppression as documented with therapeutic tacrolimus levels over the course of 7 years post LT. Though a causative relationship between COVID-19 and rejection cannot be definitively established, the timing of infection and rejection, and lack of other classical risk factors for ACR (inadequate immunosuppression, history of autoimmune liver disease, prior rejection episodes) or other infectious and metabolic triggers, infer a likely association between the two.This case highlights the importance of careful monitoring of allograft function in setting of COVID-19 infection.



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1131-A | DEVELOPMENT OF CLINICAL ALGORITHM UTILIZING VIBRATION CONTROLLED TRANSIENT ELASTOGRAPHY TO DETECT ADVANCED HEPATIC FIBROSIS IN LIVER TRANSPLANT RECIPIENTS

Dylan Vainer[1], Tamoore Arshad[2], Hiba Khan[1], Alok Baral[1], Shreya Garg[1], Audrey Ang[1], Vaishali Patel[1], Vinay Kumaran[1], David Anthony Bruno[1], Seung Lee[1], Amit Sharma[1], Mark Dhinesh Muthiah[3], Anh Bui[2] and Mohammad S. Siddiqui[1], (1)Virginia Commonwealth University Health System, (2)Virginia Commonwealth University, (3)National University Health System (NUHS)

Background: Vibration controlled transient elastography (VCTE) based liver stiffness measurement (LSM) is an excellent 'rule-out' test for advanced hepatic fibrosis in liver transplant (LT) recipients, however, its ability to 'rule-in' the disease is suboptimal. While supplementing LSM with bio-clinical data has provided promising results (i.e. FAST, Agile 3/4), they have not resulted in similar improvement in diagnostic performance when compared to LSM alone, due to the altered physiology of the LT recipients. This study aimed to improve diagnostic performance of LSM in LT recipients. **Methods:** Adult

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LT recipients with a liver biopsy and VCTE were included (N = 150). Sequential covering analysis (SCA) was performed to create rules to identify patients at low or high risk for advanced fibrosis (stage 3-4). The rules created via SCA were then compared to LSM alone at 'ruling in' and 'ruling out' advanced fibrosis. **Results:** The rules created via SCA are depicted in Figure 1A. Advanced hepatic fibrosis was definitively excluded in patients with either LSM < 7.45kPa (n = 72) or 7.45 ≤ LSM < 12.1kPa and time from LT < 5.6 years (n = 25). Conversely, likelihood of advanced fibrosis was 95% if patients had LSM > 14.1 and controlled attenuation parameter ≤ 279dB/m (n = 21). Thus, 118 (79%) were correctly identified and 32 (21%) would have required a biopsy to establish the diagnosis. Compared to previously established LSM based cutoff values of 10.5 kPa (Youden index) and 13.3 kPa (maximized specificity), the false positive rates of sequential covering analysis was 1% compared to 16.5% with LSM ≥ 10.5 kPa and 8.3% with LSM ≥ 13.3 kPa. The true positive rates were comparable at 87% for sequential covering analysis, 93% for LSM ≥ 10.5 kPa and 83% for LSM ≥ 13.3kPa. Implementing SCA lead to correct characterization of 65% of patients who were ruled out for advanced fibrosis with 100% accuracy (Figure 1B) and 14% of patients who were ruled in for advanced fibrosis with 95% positive predictive value. The intermediate zone consisted of 21% of the cohort with a 28% prevalence of advanced hepatic fibrosis. The developed sequential covering analysis approach was validated using leave 1-out cross validation with similar diagnostic performance. **Conclusion:** The proposed clinical sequential covering analysis allows for better risk stratification when evaluating for advanced fibrosis in LT recipients compared to LSM alone. Additional efforts are necessary to further reduce the number of patients with indeterminate results in whom a liver biopsy may be required.

Figure 1A

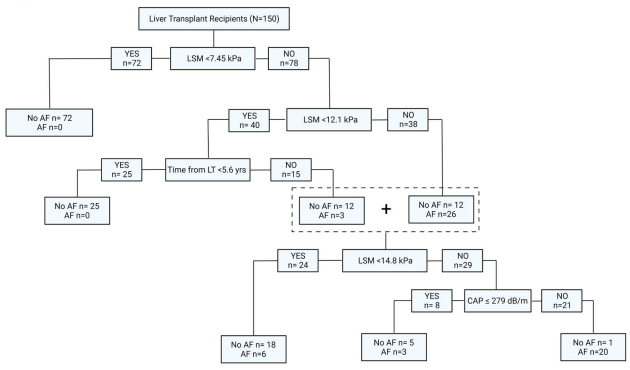
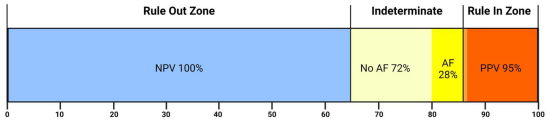


Figure 1B



Disclosures: The following people have nothing to disclose: Dylan Vainer, Hiba Khan, Alok Baral, Shreya Garg, Audrey Ang, Vaishali Patel, Vinay Kumaran, David Anthony Bruno, Seung Lee, Amit Sharma, Mohammad S. Siddiqui
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1132-A | EARLY ALCOHOL RELAPSE IN LIVER TRANSPLANT RECIPIENTS ASSOCIATED WITH SIGNIFICANT HEPATIC FIBROSIS

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Background: Alcohol relapse (AR) after liver transplant (LT) has been associated with graft loss and diminished survival. Post-LT patient fibrosis in the setting of alcohol relapse is not well described. Our aim was to examine the effects of AR on graft fibrosis and evaluate whether noninvasive scoring systems can estimate fibrosis in these patients. **Methods:** This is a retrospective study with patients who underwent LT for a primary indication of alcoholic liver disease (ALD) at a single large academic transplant center between January 2015 and October 2022. Data collected include demographics, psychosocial variables, presence and timing of AR, lab values to calculate APRI and FIB4 scores, and liver biopsy findings. Comparisons between AR and non-AR patients were made using Chi-square and two sample t-tests. **Results:** Of 159 total patients transplanted for ALD, 36 (23%) had AR post-LT. AR occurred at a median of 348 days, with 64% of AR occurring within 1 year post-LT. Predictors of AR included pre-LT psychiatric diagnosis (OR 7.9, $p < 0.01$) or medication use (OR 10.6, $p < 0.01$) and failed alcohol rehab pretransplant (OR 10.2, $p < 0.01$). Among 72 patients with liver biopsies, 18% had stage 2-4 fibrosis (significant fibrosis or SF) and 85% of SF was seen within 2 years of LT. Three patients had ≥ F3 fibrosis, two due to recurrent alcoholic hepatitis and one due to chronic rejection. In the entire cohort, SF was present in 29% of AR vs. 13% of non-AR patients ($p = 0.08$). After excluding biopsies that showed fibrosis due to acute cellular rejection, AR was associated with increased risk of SF (33% AR vs. 4% non-AR, $p < 0.01$). Patients with SF had higher mean APRI (2.0 vs 0.9, $p = 0.03$) and higher mean FIB-4 (4.2 vs 2.4, $p < 0.05$) scores. **Conclusion:** Post-LT AR is associated with increased risk of SF (33%) within 2 years of transplant. As most liver biopsies were prompted by abnormal liver-associated enzymes, the true burden of SF may be

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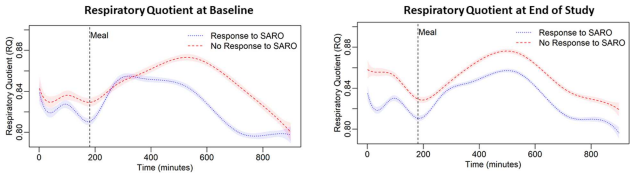
1138-A | METABOLIC FLEXIBILITY PREDICTS RESPONSE TO SAROGLITAZAR TREATMENT IN LIVER TRANSPLANT RECIPIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Mohammad S. Siddiqui[1], Deven Mr V. Parmar[2], Farheen Shaikh[3], Nihal Shaikh[3], Anh Bui[1], Vaishali Patel[4] and Arun Sanyal[5], (1)Virginia Commonwealth University, (2)Zydus Cadila, (3)Zydus Therapeutics, (4) Virginia Commonwealth University Health System, (5) Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA

Background: Metabolic flexibility is the ability to match biofuel availability to utilization with the carbohydrate being the major fuel source in the fed state and fatty acids in the fasted state. Metabolic *inflexibility*, refers to reduced ability to readily transition between fuel sources. In liver transplant (LT) recipients, reduced metabolic flexibility has been associated with non-alcoholic fatty liver disease and future risk of weight gain. Currently, there is no data in interaction between metabolic flexibility and pharmacological intervention. **Methods:** In this proof of concept, open-label trial, single-arm study, 15 adult patients with NAFLD as determined by controlled attenuation parameter were treated with saroglitazar magnesium 4mg daily for 24 weeks. Key exclusion criteria included graft cirrhosis, more than mild alcohol use, GFR < 60, and concomitant use of GLP-1 receptor agonists. Metabolic flexibility was measured at baseline and end of treatment (EOT) using whole room calorimetry and expressed as respiratory quotient (RQ). Peak RQ represents maximal carbohydrate metabolism and occurs in the post-prandial state, while trough RQ represents maximal fatty acid metabolism occurring in the fasted state. **Results:** In the overall cohort, a numerical improvement in RQ was noted from baseline and EOT, however, this did not reach statistical significance. Baseline metabolic flexibility was associated with likelihood of treatment response as defined by at least 5% reduction in liver fat from baseline to EOT (Figure 1). More specifically, responders had shorter time to peak RQ (275 ± 82 vs. 388 ± 82 minutes $p = 0.03$). An improvement in time to peak was noted in responders (275 ± 82 to 246 ± 65 min) and non-responders (388 ± 82 to 281 ± 97 min) from baseline to EOT, however, this did not reach statistical significance. Finally, lower resting RQ was noted in patients who were more likely to respond to saroglitazar than non-responders. **Conclusion:** In LT recipients, baseline metabolic flexibility predicts response to saroglitazar, first in LT population. While the current study was not designed to evaluate the impact of saroglitazar on metabolic flexibility, it does provide empiric data suggesting the impact of saroglitazar on liver fat is independent of metabolic flexibility. Moreover, the data would also suggest a potential positive effect of saroglitazar on metabolic flexibility, however, well designed studies are required to better evaluate this relationship.



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1139-A | PALLIATIVE CARE IN PATIENTS WITH BCLC-D HEPATOCELLULAR CARCINOMA LIVER TRANSPLANTATION-INELIGIBLE: RESULTS FROM A SURVEY AMONG ITALIAN HEPATOLOGISTS AND PALLIATIVE CARE PHYSICIANS

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Background: Delays and limitations of palliative care (PC) in patient with Barcelona Clinic Liver Cancer (BCLC) D hepatocellular carcinoma (HCC) liver transplantation (LT)-*ineligible* may be explained by different perceptions between hepatologists and PC physicians in the absence of shared guidelines. We aimed to assess clinicians' attitudes towards PC in BCLC-D HCC. **Methods:** Members of the Italian Association for the Study of Liver Disease (AISF) and the Italian Society of Palliative Care (SICP) were invited to a web-based survey consisting of 17 questions to investigate the general approach, the management of cirrhosis complications and pain palliation in patients with BCLC-D HCC **Results:** A total of 97 hepatologists and 70 PC physicians completed the survey: $>80\%$ of both categories currently follow 1-19 patients with LT-*ineligible* BCLC-D HCC. Moreover, 58% of hepatologists collaborates with PC physicians in the management of BCLC-D patients, while the 55% of PC physicians takes care of patients independently. Management of cirrhosis and its complications, such as administration of albumin or prescription of esophagogastroduodenoscopy, anticoagulation and antiviral treatments or indication for paracentesis, differed significantly between the two groups (Table 1). Both hepatologists and PC physicians (42% and 64% respectively) prefer to avoid NSAIDs for pain control, while full-dose acetaminophen is widely used among hepatologists, but only in few among PC physicians (64% vs 26%, $p<0.001$). Opioids are commonly used by both categories, generally (61% and 67.4%, respectively) used at full dosage, regardless of patient's liver function. **Conclusion:** This survey highlights significant differences in the approach to patients with BCLC-D HCC LT-*ineligible*, between hepatologists and PC physicians, reinforcing the need for both studies dedicated to palliative care and shared guidelines among specialists.

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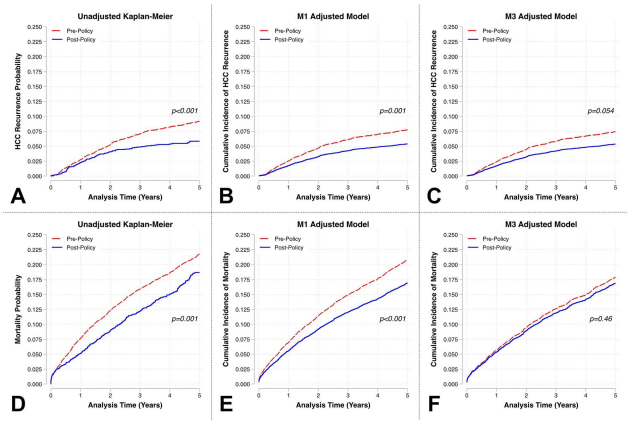
recurrence and mortality between policy eras, and sequential Cox regression models were performed for adjusted analyses. Competing risks were accounted for where applicable. **Results:** A total 7,940 patients were included, 5,879 (74.0%) pre-policy and 2,061 (26.0%) post-policy. Post-policy patients were older, more likely to have non-alcoholic fatty liver disease, received more LRT, and had lower AFP levels and smaller tumor sizes at transplant. Post-policy era was associated with an unadjusted 35% reduction in risk of post-LT HCC recurrence (HR 0.65, 95% CI 0.52-0.80, $p < 0.001$; Figure 1A). After adjusting for tumor characteristics at listing this association remained (SHR 0.69, 95% CI 0.55-0.86, $p = 0.001$; Figure 1B), however after additionally adjusting for LRT episodes and RETREAT score, there was no longer a statistically significant association (SHR 0.77, 95% CI 0.59-1.00, $p = 0.054$; Figure 1C). Similarly, in unadjusted analysis, there was a significant reduction in mortality associated with post-policy era (HR 0.81, 95% CI 0.72-0.92, $p = 0.001$; Figure 1D), but this association was null after comprehensive covariate adjustment (SHR 0.94, 95% CI 0.80-1.11, $p = 0.46$; Figure 1F). **Conclusion:** We observed a significant reduction in post-LT HCC recurrence and mortality after policy implementation. Sequential analyses demonstrate that this difference is likely mediated through waitlist selection of relatively healthier patients, increased opportunity for LRT use, and potential selection of favorable tumor biology.



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Maarouf A. Hoteit – HepQuant, LLC: Consultant, No, No;
K Rajender Rajender Reddy – BMS: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Mallinckrodt Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Sequana: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Grifols: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Exact Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; HCC-TARGET: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; NASH-TARGET: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Spark Therapeutics: Consultant, No, No; Novo Nordisk: Consultant, No, No; Genfit: Consultant, No, No; BioVie: Consultant, No, No; Novartis: Advisor, No, No; Astra Zeneca: Advisor, No, No; Associate Editor Gastroenterology: Executive role , No, No; UptoDate: Royalties or patent beneficiary, No, No;
The following people have nothing to disclose: Lina Yagan, Peter Abt, Samir Abu-Gazala

1143-A | UTILITY OF SCORES TO PREDICT ALCOHOL USE AFTER LIVER TRANSPLANT (LT): TAKE THEM WITH A GRAIN OF SALT

Kevin Houston[1], Nikki Duong[2], Richard K. Sterling[1], Amon Asgharpour[1], Sheila Bullock[1], Stephan Weinland[1], Nicole Keller[1], Ekaterina Smirnova[1], Hiba Khan[1], Scott C. Matherly[1], Joel P. Wedd[1], Hannah Lee[1], Mohammad S. Siddiqui[1], Vaishali Patel[1], Vinay Kumaran[1], Seung Lee[1], Amit Sharma[1], Aamir Khan[1],

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

Daisuke Imai[1], Marlon Levy[1] and David Anthony Bruno[1], (1)Virginia Commonwealth University Health System, (2)Virginia Commonwealth University

Background: Traditionally, LT programs required 6-months (M) of abstinence prior to listing in alcohol-associated liver disease (ALD). Recently, LT has been offered to those with < 6M sobriety including those with acute alcohol-associated hepatitis (AH). The Sustained Alcohol use post-Liver Transplant (SALT) and the High-Risk Alcohol Relapse (HRAR) scores were developed to predict return to alcohol use after LT. However, their utility is controversial. Our aim was to assess the utility of these scores to predict alcohol use after LT in those with ALD. **Methods:** A retrospective analysis of deceased donor LT 10/2018 to 4/2022 was performed. Demographic, clinical, and laboratory data were collected. All patients (pts) underwent careful pre-LT psychosocial evaluation. Data on alcohol use, substance abuse, prior rehabilitation, and legal issues were collected. Post-LT, all were encouraged to participate in rehabilitation programs and underwent random PeTH testing. Pts with ALD were stratified by < or > 6M sobriety prior to listing. Those with < 6M were further stratified as acute AH by NIAAA criteria and non-AH. The primary outcome was utility of the SALT and HRAR scores to predict return to alcohol use (+ PeTH) within 1 year after LT. **Results:** Of the 365 LT, 171 were for ALD: 86 had > 6M sobriety and 85 had < 6M sobriety; 41 with AH and 44 non-AH. Demographics, clinical, and psychosocial characteristics among these groups are shown (Table). Those with < 6M sobriety were younger, less likely African American, had higher MELD-Na and on the transplant waiting list for fewer days. In those with AH, the mean time of abstinence to LT was 58d, 71%% failed prior rehabilitation. One-year survival was similar among the 3 groups (90-93%). Following LT, return to drinking was similar in the AH (24%) compared to < 6M non-AH (15%) and > 6M ALD (22%). Only 4% had return to heavy drinking. The accuracy of the SALT score to predict return to alcohol was low (accuracy 0.63) with poor sensitivity (46%), specificity (68%), and positive predictive value (26%) with good negative predictive value (83%). HRAR had similar utility: accuracy (0.61), Sens 37%, Sp 67%, PPV 22%, and NPV 81%. **Conclusion:** In carefully selected pts undergoing LT for ALD with post-LT AALD counseling, while 1-yr survival was excellent, return to any drinking was observed in 15-24%, with heavy drinking in only 4%. Both SALT and HRAR scores had good NPV in identifying pts at low risk for recidivism.

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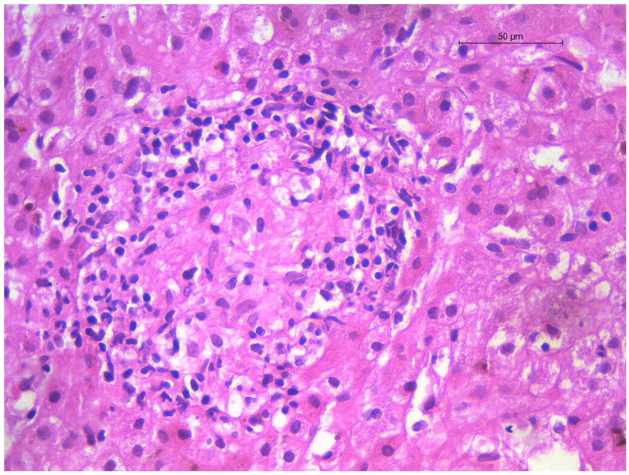
1144-A | VIBRATION CONTROLLED TRANSIENT ELASTOGRAPHY BASED PARAMETERS PREDICTS CLINICAL OUTCOMES IN LIVER TRANSPLANT RECIPIENTS

Alok Baral[1], Shreya Garg[1], Audrey Ang[1], Madison Nguyen[1], Rehan Razzaq[1], Tamoore Arshad[2], Hiba Khan[1], Ian O'Connor[1], Siddiq Elmahdi[1], Michael Tseng[1], Vaishali Patel[1], Anh Bui[2] and Mohammad S. Siddiqui[2], (1)Virginia Commonwealth University Health System, (2)Virginia Commonwealth University

Background: Liver stiffness measurement (LSM), a surrogate measure of hepatic fibrosis, can be readily measured via vibration controlled transient elastography (VCTE) as a point of care test. LSM has been validated for detection of advanced hepatic fibrosis in liver transplant (LT) recipients. However, it is currently not known if LSM can predict risk of clinical outcomes. Thus, the present study aimed to evaluate the relationship between LSM and clinical outcomes. **Methods:** The study included adult LT recipients (N = 342) who had a successful VCTE between 2015 and 2022 for routine clinical care. VCTE was performed after an overnight fast and a cutoff value of LSM ≥ 10.5 kPa was used for significant fibrosis, while a controlled attenuation parameter (CAP) ≥ 270 dB/m was used for presence of hepatic steatosis based on prior published literature. Patients with history of end organ damage (i.e. heart failure, renal failure requiring HD, liver graft failure etc.) were excluded. The primary outcome of the study was all-cause mortality. The secondary outcomes included new-onset coronary artery disease (CAD), myocardial infraction (MI), and graft cirrhosis. Multivariate Cox regression models were constructed that included body mass index, age, gender, diabetes status and etiology of liver disease as covariates. **Results:** The study cohort included 67 (19.6%) patients with LSM ≥ 10.5kPa. The median time from LT to VCTE was 68.1 (IQR 21.5, 144.6) months. A total of 59 LT recipients died over a median follow up of 34.6 (IQR 25.4, 55.4) months. Baseline LSM was a strong and statistically significant predictor of all-cause mortality (Figure 1A). The relationship between LSM and all-cause mortality remained significant in multivariate modeling with HR of 2.14 (95% CI 1.25, 3.66, $p = 0.006$). LSM was not associated with future risk of MI or development of CAD. No interaction between choice of immunosuppression (cyclosporine vs. tacrolimus) and LSM and mortality were noted. Finally, a strong independent relationship between CAP and

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

alcoholic fatty liver disease (NAFLD). 9% of the subjects presented with a focal liver space occupying lesion (SOL). All the cirrhotic subjects presented with either acute decompensation of cirrhosis (AD) / acute on chronic liver failure (ACLF) and in them, tuberculosis was postulated as an acute inciting event. 86% of subjects underwent liver biopsy, granuloma were identified in all of them. 10% of the samples were sent for cultures. Three (3) subjects, expired during the study period. Of them two were cirrhotic beforehand, and presented with ACLF. Mean time from symptom onset to start of therapy was 6.8 months. Standard 1st line quadruple therapy could only be offered to 27% of the subjects at the initiation. 63% of the subjects afterwards received complete 1st line therapy. **Conclusion:** Hepatic tuberculosis can present with a constellation of symptoms and signs. Identification and diagnosis, requires good clinical acumen. Tissue diagnosis aids in the diagnosis and must be offered to all suspected individual's. In subjects with underlying chronic liver disease, t = hepatic tuberculosis might precipitate acute decompensation and can often prove fatal.



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Disclosure information not available at the time of publication: Ranajoy Ghosh, Dipankar Mondal, Srijan Mazumdar, Kishalaya.

◆ 1222-C | HEPATITIS DELTA TESTING TRENDS IN THE U.S. VETERANS AFFAIRS MEDICAL SYSTEM (2000-2022): AN ANALYSIS OF PATIENT AND PROVIDER-LEVEL PREDICTIVE FACTORS

Binu V John[1], Mahmoud Manouchehri Amoli[2], Robert J. Wong[3], Donna M. Evon[4], Bassam Dahman[2] and VALID group of investigators, (1)University of Miami and Miami VA, (2)Virginia Commonwealth University, (3)VA Palo Alto Healthcare System, (4)University of North Carolina

Background: Low prevalence of Hepatitis Delta Virus (HDV) infection in the US could be attributed to insufficient testing, which can result in an underestimation of true prevalence. This study aimed to identify prevalence and factors associated with HDV testing among participants with positive Hepatitis B surface antigen (HBsAg) in the Veterans Health Administration (VHA). **Methods:** This was a nationwide retrospective study involving all participants positive for HBsAg between 01/2000 and 12/2022 within the VHA. We identified those who were tested, and positive for HDV, and used a logistic regression model to identify patient and provider-level predictive factors associated with HDV testing. **Results:** Of 67,606 participants with a positive HBsAg, 4,661(6.9%) were tested at least once for HDV antibodies, of which 333 (7.1%) were positive (298 HDV RNA positive). The annual number of HDV antibody tests ordered in the VHA was stable from 2000 to 2015 (135-171 a year), increased by over 50% from that baseline in 2016-2017 (283 and 277 respectively), and more than doubled in 2018-2019 (451 and 446 respectively), before dropping during COVID-19 from 2020-2022 (231, 289 and 244 respectively). Participants in the Northeast (aOR 1.31, 95% CI 1.18-1.45, $p < 0.001$) were more likely, while those in the Midwest (aOR 0.69, 95% CI 0.60-0.79, $p < 0.001$) were less likely to undergo HDV testing. Participants received care at an academic VA (aOR 1.24, 95% CI 1.1-1.4, $p < 0.001$) or from a hepatology provider (aOR 1.43, 95% CI 1.29-1.60, $p < 0.001$) were more likely, while those under the care of a primary care provider were less likely to be tested for HDV (aOR 0.62, 95% CI 0.52-0.73, $p < 0.001$). Non-Hispanic Black people were less likely to be HDV tested (aOR 0.87, 95% CI 0.79-0.95, $p = 0.004$)-however, no difference in screening among other racial groups were observed. Participants with private insurance coverage (aOR 1.18, 95% CI 1.09-1.27, $p < 0.004$), and those Medicaid eligible (aOR 1.60, 95% CI 1.25-2.04, $p < 0.001$) were more likely to be tested, as were those on oral nucleotide/nucleoside therapy (aOR 1.58, 95% CI 1.45-1.72, $p < 0.001$), participants with cirrhosis (aOR 1.12, 95% CI 1.01-1.25, $p = 0.04$), and hepatic decompensation (aOR 1.28, 95% CI 1.10-1.49, $p = 0.002$). Lastly, HDV testing was positively associated with being tested for HBeAg, HBeAb, and HBcIgM. In contrast, HCV positive (aOR 0.90, 95% CI 0.81-0.98, $p = 0.02$) and HIV positive participants (aOR 0.78, 95% CI 0.69-0.87, $p < 0.001$) were less likely to be tested for HDV. **Conclusion:** While overall HDV screening rates have increased in the VHA, participants who are Black, living in the Midwest, receiving liver care from a primary care provider, those at high risk of HDV, as well as HIV or HCV positive patients are less likely to be tested for

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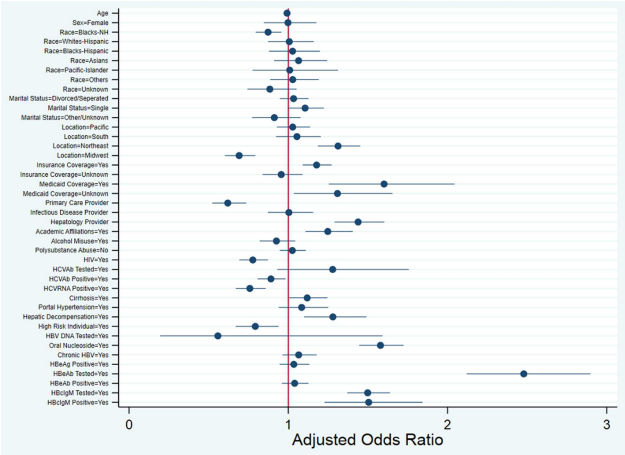
HDV. These results highlight the need for refining testing strategies to increase HDV screening rates, especially among historically marginalized and high-risk populations.



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Donna M. Evon – HighTide Therapeutics: Consultant, No, Yes;
Bassam Dahman – Exact Sciences: Consultant, No, Yes;
The following people have nothing to disclose: Mahmoud Manouchehri Amoli

1223-C | HEPATITIS DELTA VIRUS SCREENING STRATEGIES IN FRENCH UNIVERSITY HOSPITAL LABORATORIES: ADVOCACY FOR REFLEX TESTING IMPLEMENTATION

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Background: Infection with Hepatitis delta virus (HDV) leads to the most severe form of chronic viral hepatitis; unfortunately, screening rates are scarce in most areas and patients are often diagnosed at an advanced clinical stage. International guidelines recommend either a systematic HDV screening for all HBsAg-positive patients (EASL) or a risk-based approach (AALSD). In addition to perform HDV serology on medical prescription, some laboratories have implemented a "HDV reflex testing" protocol, consisting of the addition of a serological HDV test on all samples with a first HBsAg positive result. The aim of this cross-sectional study was to analyse the different strategies implemented in seven French university hospital laboratories and to compare their efficiency for HDV antibody (HDV-Ab) and viral load (HDV-VL) screening. **Methods:** All individual's with a positive HBsAg test referred for the first time between January 2018 and October 2022 were included. Patients replicate requests were removed. Total or IgG HDV-Abs were assayed with commercial tests, HDV-VL with in-house or commercial tests, and HDV genotype with partial sequencing (R0 region). **Results:** Of 459,644 consecutive individual's, 6,772 were tested HBsAg-positive for the first time (mean age 38.7, sex ratio 2.03). Testing for HDV-Abs was conducted on 5,749 patients (84.9%) and 364 of them were positive (6.3%, CI 95%: 5.7-7.0, mean age 40.9, sex ratio 2.36). HDV-VL was determined in 285 (78.3%) patients and 167 (58.6%, CI 95%: 52.8-64.2) had an active HDV infection. HDV-1 genotype was predominant (77%), followed by HDV-5 (19%). The screening rate was 46.6% in one centre (pre-reflex testing period), varied from 65.2% to 96.4% in laboratories with a manual add-on strategy (i.e. biologist-driven, 5 centres), and reached up to 99.2% when the HDV-Ab reflex testing is automatically set in the local

prolonged duration of NA and was greatest among those with low HBsAg. These data demonstrate the utility of HBsAg kinetics and can predict time to functional cure for those receiving NA, although further studies are required.
Disclosures: Scott K. Fung – Gilead Sciences, Inc.: Speaking and Teaching, No, No; AbbVie: Speaking and Teaching, No, No; Lupin: Speaking and Teaching, No, No; Gilead Sciences, Inc.: Advisor, No, No; AbbVie: Advisor, No, No; Novo Nordisk: Advisor, No, No; Pfizer: Advisor, No, No; Gilead Sciences, Inc.: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No;
The following people have nothing to disclose: Yong Gyu Hyun

1319-C | LOWER VIRAL DIVERSITY OF THE HEPATITIS B CORE GENE IS ASSOCIATED WITH A DECREASED LIKELIHOOD OF HBEAG CLEARANCE IN IMMUNE-TOLERANT PATIENTS

Tai-Chung Tseng, Chun-Jen Liu, Tung-Hung Su, Hung-Chih Yang, Pei-Jer Chen and Jia-Horng Kao, National Taiwan University Hospital

Background: Current criteria for defining immune-tolerant patients rely on serum ALT and HBV DNA levels. However, these markers can fluctuate, making it challenging to distinguish immune-tolerant patients from from immune-active individual's who may exhibit normal ALT levels temporarily. As viral quasispecies arise from the adaptation to selection pressure exerted by the host immune response, our objective was to investigate whether lower viral diversity could serve as an indicator to identify genuine immune-tolerant patients. **Methods:** We conducted a retrospective study involving 202 HBeAg-positive patients with HBV DNA levels exceeding 1 million IU/mL and ALT levels below the upper limits of normal defined by the AASLD guidelines. These patients were classified as immune-tolerant based on the AASLD criteria and were enrolled between 1985 and 1990. Throughout the HBeAg-positive stage, these patients remained untreated. The primary endpoint of the study was HBeAg seroclearance. Serum samples collected at enrollment were used to determine viral factors. Viral quasispecies of the hepatitis B core (HBc) gene were determined using deep sequencing, with the ability to detect viral variants as low as 0.1%. We defined high and low viral diversity using a cutoff of 0.005. **Results:** Among the 202 immune-tolerant patients, the mean age was 31.2 years, with 56.9% being male. A total of 13.3% of patients exhibited high HBc viral diversity. Over a mean follow-up period of 15.2 years, 88 patients achieved HBeAg seroclearance, resulting in an annual incidence of 2.9%. Univariable analysis demonstrated that older age and higher HBc diversity were associated with an increased probability of clearing HBeAg. Compared to patients with low HBc diversity, those with higher diversity had an elevated chance of clearing HBeAg, with a hazard ratio (HR) of 2.62 (95% CI: 1.58-4.36). Multivariable analysis revealed that higher HBc diversity remained an independent factor, with an HR of 2.32 (95% CI: 1.37-3.95), even after adjusting for age, sex, HBV DNA levels, and HBV genotype. This relationship remained significant, even when restricted to 165 immune-tolerant patients under the age of 40. **Conclusion:** In a cohort of immune-tolerant patients defined by HBV DNA and ALT levels according to the AASLD guideline, lower HBc viral diversity was associated with a reduced likelihood of clearing HBeAg. Deep sequencing-based determination of viral diversity may aid in the identification of genuine immune-tolerant patients.
Disclosures: The following people have nothing to disclose: Tai-Chung Tseng, Chun-Jen Liu, Tung-Hung Su, Hung-Chih Yang, Pei-Jer Chen, Jia-Horng Kao

1320-C | METABOLOMIC PROFILING TO PREDICT HISTOLOGIC PROGRESSION OF LIVER FIBROSIS IN PATIENTS WITH HIV AND HBV COINFECTION

Tzu-Hao (Howard) Lee, Baylor College of Medicine, Richard K. Sterling, Virginia Commonwealth University Health System, Joseph E Lucas, Vital Statistics, Wendy C King, University of Pittsburgh, Keyur Patel, University Health Network, Toronto, ON, Canada and Susanna Naggie, Duke Clinical Research Institute, Durham, NC

Background: Despite antiretroviral therapy (ART), some patients with HIV-HBV coinfection still have advanced fibrosis or fibrosis progression. Multiple metabolic pathways have been implicated in liver disease pathogenesis. Our study aims to discover expression patterns of circulating bioactive metabolites and their association with liver fibrosis in patients with HIV-HBV coinfection. **Methods:** This study cohort includes adults with HIV-HBV coinfection on ART recruited from eight Hepatitis B Research Network (HBRN) sites in North America. Clinical data, plasma samples, and liver biopsy were collected at entry, with paired liver biopsy obtained three or more years later. Serum samples within 24 weeks of the baseline liver biopsy were used to quantify 325 metabolites including fatty acids, amino acids, bile acids, and related intermediate metabolites. Metabolite expression was adjusted by clinical factors including sex, age, BMI, viral

loads, HCV/HDV coinfection, and medications for HIV, diabetes, and dyslipidemia to assess for association with (1) advanced fibrosis (Ishak fibrosis score greater than 3) in baseline liver biopsy and (2) worsening Ishak score on paired liver biopsy. We used generally applicable gene set enrichment (GAGE) pathway analysis to test for aggregate changes in the expression of metabolites grouped by predefined class. **Results:** 108 participants were included in the study, with a mean age of 50 years. 80% of participants had HBV DNA < 200 (IU/ml), and 92% had HIV RNA < 200 (copies/ml) with a median CD4 369 (cells/mm3). Ten participants (9.3%) had advanced fibrosis at baseline liver biopsy. In pathway analysis, metabolites in the amino acid class were associated with baseline advanced fibrosis (Table). 60 participants had paired liver biopsies (median 3.6 y apart) with 11 (18%) exhibiting fibrosis progression. Baseline serum expression of Dodecanedioic acid (DiCA [12:0]), cysteine synthesis indicator, and the sum of neurotransmitter expression (dopamine, histamine, and serotonin) was associated with fibrosis progression in the paired liver biopsy. In the pathway analysis, multiple classes of metabolites were associated with progression of fibrosis (Table). **Conclusion:** In participants with HIV-HBV coinfection, approximately 1 in 5 exhibited progression of fibrosis despite ART. We identified several baseline metabolites classes associated with the progression of liver fibrosis. Further discovery could elucidate pathways and biomarkers predictive of liver disease in this high-risk group.

Table: Metabolites classes associated with liver fibrosis and fibrosis progression in pathway analysis

Metabolites Classes and associated outcome	P-Value	Number of metabolites with positive correlation	Numbers of metabolites with negative correlation	*False discovery Rate
Baseline Liver Fibrosis				
Amino Acids	0.00248	3	7	7.9%
Liver Fibrosis Progression				
Triacylglycerols	<0.00001	226	16	<0.1%
Alcohols	0.00017	24	1	0.2%
Carboxylic Acids	0.00034	6	1	0.2%
Glycerophospholipids	0.00037	77	10	0.2%
Fatty Acids	0.00091	12	0	0.5%
Biogenic Amines	0.00100	6	3	0.5%
Epoxide	0.00377	1	2	1.5%
Hydroxyperoxide	0.00622	3	0	2.2%
Sugars	0.01573	0	1	5.0%
Acylcarnitines	0.02088	33	7	6.1%

* False discovery rate (FDR) is a control measure for high-throughput data. FDR is defined as the expected ratio of false positive classifications to the total number of positive classifications. For the purpose of novel hypotheses, an FDR of less than 10% is considered valid. We used Benjamini-Hochberg to control the false discovery rate.

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The following people have nothing to disclose: Tzu-Hao (Howard) Lee, Richard K. Sterling
Disclosure information not available at the time of publication: Joseph E Lucas, Wendy C King, Susanna Naggie

1321-C | MIR-4461 ASSOCIATED WITH HEPATITIS B-DERIVED HEPATOCELLULAR CARCINOMAS

Aiko Sakai and Masaya Sugiyama, National Center for Global Health and Medicine

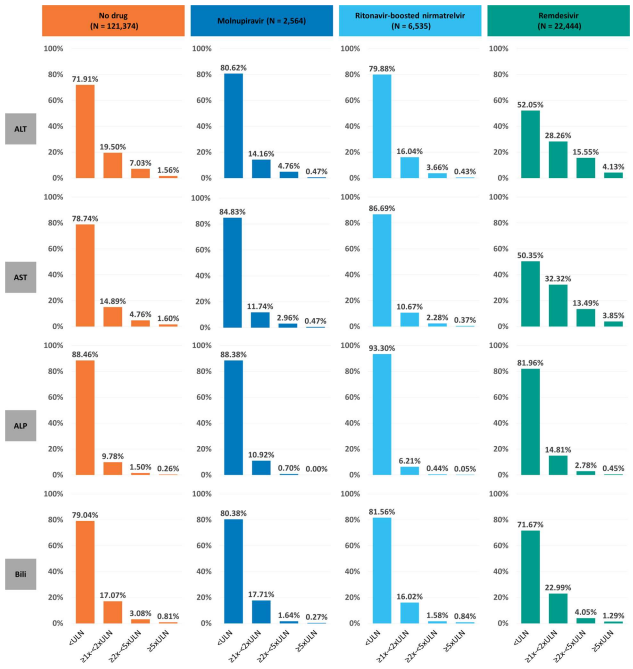
Background: The development of hepatocellular carcinoma (HCC) due to hepatitis B is difficult to predict. One reason is that its pathogenesis is not due to a persistent accumulation of inflammation. The molecular changes that occur in cells persistently infected with hepatitis B virus (HBV) are not clear on a cell-by-cell basis. The impact of those HBV-infected cells on the pathogenesis of the disease is also unknown. In this study, single-cell RNA-seq (scRNA-seq) analysis of HBV-infected cells was performed to investigate changes in gene expression on a single-cell basis. The molecules relating to HCC were identified and their functions were analysed. **Methods:** After the infection of primary hepatocytes with HBV, their scRNA-seq analysis was performed. scRNA-seq data were compared between HBV RNA-positive and negative hepatocytes (cell populations in the same environment) in one dish. The miR-4461 levels of HuH7 and HepG2 cells with and without HBV were identified and analyzed for cell proliferation, invasion and migratory capacity. Target genes to which miR-4461 bound were explored by in vitro assay. miR-44661 was quantified in HCC and non-HCC areas using resected liver tissue of hepatitis B and non-B/non-C. **Results:** Primary hepatocytes were infected with HBV and then scRNA-seq was performed. miR-4461 was significantly reduced in HBV-infected hepatocytes. miR-4461 expression was reduced when HBV replication plasmids were transfected into HuH7 and HepG2 cells. siRNA knockdown of miR-4461 enhanced the proliferation, invasive and migratory capacity of HuH7 and HepG2 cells. miR-4461 expression levels were confirmed in liver tissues from hepatitis B and non-B/non-C HCC patients. In non-B/non-C specimens, no difference of the miR-4461 expression was observed in both HCC and non-HCC areas compared to normal liver tissue. On the other hand, in hepatitis B specimens, the expression of miR-4461 was lower than that of normal liver ($p < 0.05$). in addition, the expression in HCC areas was lower than non-HCC areas ($p < 0.05$). Target genes of miR-4461 were explored using database and in vitro assay. Then, the FGA gene was one of the targets of miR-4461. **Conclusion:** The miR-4461 pathway was suggested to be associated with the establishment and pathogenesis of HBV infection. miR-4461 levels were reduced in liver tissue derived from hepatitis B, and a more significant reduction was observed in HCC area, suggesting that this pathway could be a useful biomarker for HBV-derived HCC.
Disclosures: The following people have nothing to disclose: Aiko Sakai, Masaya Sugiyama

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

1737-A | RISK OF DRUG-INDUCED LIVER INJURY WITH REMDESIVIR, MOLNUPIRAVIR AND RITONAVIR-BOOSTED NIRMATRELVIR IN PATIENTS WITH CHRONIC LIVER DISEASE

Binu V John[1], Dustin R Bastaich[2], K Rajender Rajender Reddy[3], Ashwani K. Singal[4], Bassam Dahman[2] and VALID group of investigators , (1)University of Miami and Miami VA, (2)Virginia Commonwealth University, (3)University of Pennsylvania, (4)University of South Dakota

Background: COVID-19 remains the sixth most common cause of death in the United States in 2023, and patients with chronic liver disease (CLD) remain at risk. Approved antivirals may be potentially hepatotoxic, while there is limited data on their safety in CLD. This study aimed to determine the risk of drug induced liver injury (DILI) with remdesivir, ritonavir boosted nirmatrelvir, and molnupiravir, in a large national cohort of participants with CLD. **Methods:** This was a retrospective cohort study of 152,917 Veterans with CLD who developed SARS-CoV-2 infection between 3/1/2020 and 12/31/2022. Participants receiving remdesivir (n = 22,444), ritonavir-boosted nirmatrelvir (n = 6535), or molnupiravir (n = 2564) within 7 days of a positive SARS-Co-V-2 PCR were compared with untreated participants with COVID-19 (n = 121,374) after controlling for potential confounders. The outcomes included mild (peak ALT > 2 times upper limit of normal [ULN]), and moderate (ALT > 5-fold ULN) elevations at 60-days from baseline values. The outcomes were modeled using multivariable Poisson regression accounting for follow-up time and adjusting for age, sex, race, BMI, Charleston Comorbidity Index, diabetes, smoking, hypertension, COPD, AUDIT-C, severity of COVID-19, and baseline lab results (ALT, AST, ALP, total bilirubin, platelet count, and creatinine). **Results:** The overall study participants were predominantly male (n = 139,978, 91.5%) and white (n = 70,436, 46.1%), with a median age of 68.6 years (IQR 15.7). The most common etiology of liver disease was NAFLD (n = 122,191, 79.9%), followed by alcohol (n = 13,468, 8.8%), and HCV (n = 11,789, 7.7%), and 9,572 (6.3%) individual's had cirrhosis. Participants who received remdesivir had a 1.19-fold higher likelihood of mild elevations in ALT (95% CO 1.14-1.24, p < 0.0001) but a lower likelihood of moderate ALT elevations (aHR 0.86, 95% CI 0.79-0.94, p = 0.001). Exposure to ritonavir-boosted nirmaltrevir was associated with a lower likelihood of mild (aHR 0.69, 95% CI 0.61-0.78, p < 0.0001) and moderate (aHR 0.59, 95% CI 0.40-0.85, p = 0.005) ALT elevations. There was no association of molnupiravir with mild (aHR 0.92, 95% CI 0.78-1.09, p = 0.36) or moderate (aHR 0.61, 95% CI 0.34-1.07, p = 0.08) elevations in ALT. **Conclusion:** In this large study of Veterans with CLD, anti-virals used to treat COVID-19 had a favorable hepatic safety profile. Compared to an untreated COVID-19 cohort, molnupiravir and ritonavir-boosted nirmatrelvir treated group did not have an increased rate of elevations in ALT, while remdesivir use was associated with only mild ALT elevations.



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1738-A | SIGNIFICANT HEPATIC FIBROSIS IN PATIENTS WITH RHEUMATOID ARTHRITIS WAS NOT ASSOCIATED WITH DURATION OF TREATMENT OR CUMULATIVE DOSE OF METHOTREXATE

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Background: Methotrexate (MTX) has been one of the main agents used for treatment of Rheumatoid Arthritis (RA) for years. Drug-induced liver injury is one of the concerns in patients on long term treatment with MTX. Based on guidelines, patients on MTX are recommended to be monitored for liver tests abnormalities and fibrosis for those on long term treatment. However, the correlation between cumulative dose of MTX and increased risk of hepatic fibrosis has been questioned by more recent studies. **Methods:** In this prospective study, 120 adult patients with RA receiving treatment with MTX for more than 6 months were recruited from Rheumatology clinics of Shiraz University of Medical Sciences and underwent liver assessment. Patients with known chronic liver disease except for fatty liver were excluded. Complete history and physical exam were done by hepatologist. Full profile liver testing, viral hepatitis serology, CBC, ultrasound and Vibration Controlled Transient Elastography (VCTE) through FibroScan were performed. **Results:** Ninety-four participants (93.6% female, mean age 53.4 $\pm$ 10.4 y) completed the study. Of them, 42.6% had received MTX for more that 10 years and in 45.7% cumulative dose of MTX was more than 4 grams. History of type 2 diabetes was reported in 17%. None of the patients had a positive serology for Hepatitis B antigen or Hepatitis C antibody, but in 5.6% Hepatitis B core antibody was positive. Ultrasound reported fatty liver in 60.6% of patients and in only one patient features of chronic liver disease were reported. VCTE was technically feasible in 74 patients. Of those, 8.1% had significant hepatic fibrosis ($F \geq 2$) and 35 (47.3%) had significant hepatic steatosis ($S \geq 2$). Body Mass Index (BMI) was significantly higher in patients in whom VCTE failed. Duration of MTX use and cumulative dose of MTX did not have statistically significant associations with significant fibrosis ($P = 0.862$ and $P = 0.983$). In multiple linear regression analysis, BMI ($P = 0.23$) and AST/PLT ratio ($P = 0.22$) were identified as independent predictors for significant hepatic fibrosis. BMI was identified as an independent risk factor for significant hepatic steatosis ($P < 0.001$). **Conclusion:** In this study, the population of patients with RA on MTX, using VCTE as a non-invasive test, no significant correlation was observed between duration of treatment or cumulative dose of MTX and significant hepatic fibrosis.
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correlate with risk factors in the psychiatric hospital patient population and population in total. Both SCC and especially shelter populations are at high risk of HCV infection. Screening tools and primary health care professionals should be made more available for these populations.
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1851-A | STRATEGIES TO ELIMINATE HEPATITIS C VIRUS INFECTION IN THE AMERICAS

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Background: Although the WHO strategy has the goal to eliminate the hepatitis C virus (HCV) as a public health threat by 2030, the existence of national strategies is variable worldwide. We aimed to assess the establishment of different policies and strategies to

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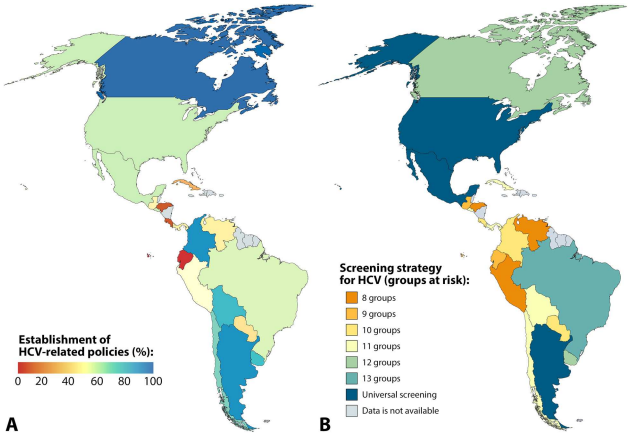
eliminate HCV in the Americas. **Methods:** We conducted a 23-item survey about HCV infection among gastroenterologists and hepatologists in the Americas. Questions were classified into four categories: policies and civil society (1 question), diagnosis (6 questions), care management (14 questions), and monitoring systems (2 questions). The survey was carried out using an electronic form between November 2022 – May 2023. Data were collected in a spreadsheet, revised by two independent reviewers, and compared with governmental institutions, regulatory agencies, scientific societies, and scientific publications. We estimated an index obtained from a regression scoring method through exploratory analysis, and row values were normalized from 0 to 100 using a min-max method. **Results:** We obtained 52 responses from 19 out of 21 countries targeted. The median HCV-related policies index was 51.4 [IQR: 27.3–70.1]. The lower establishment of HCV-related policies was observed in Ecuador (0.0), Honduras (6.6), and Costa Rica (9.8), while the highest performance was observed in Argentina (94.1), Colombia (94.7), and Canada (100) (Figure A). Fifteen (78.9%) countries have adopted a national strategic plan to eliminate HCV. Three (15.8%) countries have universal screening for HCV infection (Figure B). After a positive HCV serological test, 10 (52.6%) countries perform reflex testing to confirm HCV diagnosis using the same sample. However, only 7 (36.8%) countries have an alert system for the requesting physician. Twelve (63.2%) countries have a direct referral system for specialized care of HCV-positive cases. There is universal access to direct-acting antivirals (DAAs) in 15 (78.9%) countries. Universal access to DAAs was not widely available in Cuba, Ecuador, Venezuela, and the United States. Seven (36.8%) countries have generic DAAs available. Only 3 (15.8%) countries perform a retrospective search for HCV-positive cases that could have been lost to follow-up. **Conclusion:** Although most countries have adopted a national strategic plan to eliminate HCV, there are several issues and barriers to elimination in the Americas.



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1852-A | SUCCESSFUL SCREENING, LINKAGE TO CARE, AND TREATMENT OF HEPATITIS C IN A TINY SHELTER ENCAMPMENT ON VETERANS AFFAIRS GROUNDS

Cassandra Coleman Lautredou[1], Kimberly Lynch[2], Katherine Stricker[1], Peter Capone-Newton[2], Matthew McCoy[2], Jenna H Kawamoto[3], Arpan Arun Patel[3,4], Michele Seckington[2] and Debika Bhattacharya[3,4], (1) University of California, Los Angeles. David Geffen

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Comparison		vs	aHR (95%CL)	P
Treatment status and outcome	SVR	Untreated	0.29 (0.24, 0.35)	<.0001
		TF	0.12 (0.1, 0.16)	<.0001
	TF	Untreated	2.35 (1.97, 2.81)	<.0001
Sex	Female	Male	0.83 (0.74, 0.94)	<.01
Race	Black	White	1.5 (1.29, 1.75)	<.0001
	AAPI		0.87 (0.66, 1.16)	0.37
BMI	<25	25–30	0.70 (0.6, 0.81)	<.0001
	25–30	≥30	0.85 (0.74, 0.99)	0.04
Cirrhosis	Decompensated	Compensated	8.06 (4.85, 13.41)	<.0001
History of malignancy		No such history	1.75 (1.44, 2.11)	<.0001

aHR, adjusted hazard ratio; CL, confidence limits; SVR, sustained virological response; TF , treatment failure; AAPI, Asian American/ Pacific Islander

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1858-A | THE RELATIONSHIP OF VADOC INMATES WITH HEPATITIS C AND THE BARRIERS PREVENTING THE INITIATION OF DAA TREATMENT

Lisa Carpenter, Temple University, Shawn Lewis, Virginia Commonwealth University and Richard K. Sterling, Virginia Commonwealth University Health System

Background: To achieve global elimination of the hepatitis C virus (HCV), providing treatment to marginalized populations (e.g., incarcerated individual's) is necessary. The prevalence rate of HCV in the prison population ranges from 12-31%, compared to 1.8% for nonincarcerated individual's. Oral direct-acting antiviral (DAA) treatment is 96% effective at achieving a sustained virologic response (SVR) and can be administered over 8-12 weeks, with a significant decrease in side effects when compared to previous HCV treatments. Notwithstanding the availability of DAA treatment many prisons fail to treat all inmates who have HCV. The purpose of this study was to investigate the barriers in the Virginia Department of Corrections (VADOC) preventing the initiation of DAA treatment for inmates diagnosed with HCV. **Methods:** In this retrospective cohort study designed as a secondary analysis for the quality improvement of HCV treatment, data was collected from electronic medical records (EMR) of VADOC inmates who were referred for HCV treatment but did not start. Barriers were gathered from medical provider and VADOC staff notation in EMRs then grouped by common theme to assess frequencies. Statistical analyses were used to examine associations between treatment groups based on prison level data and demographics; no treatment = 135, initiated treatment = 2,062. **Results:** Of the inmates who had not initiated DAA treatment there were 124 (91.9%) males and 11 (8.1%) females. The mean age was 50 years old, with 44 Black (32.6%) and 89 White (65.9%) individual's. Of the 39 prisons, 26 prisons had 1 or more inmates who had not initiated DAAs (6.1% of total), ranging from 1-15 inmates per prison. Missing lab

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results (42.2%), limited time remaining in an inmate's sentence (23.7%), and missing follow-up appointments (20.0%) had the highest frequency for preventing treatment initiation. In addition, there is a significant association between prison location and treatment initiation (Chi-square $p < 0.0001$), further defined by prison regional location and population size. **Conclusion:** With the increase in frequency of prison-initiated barriers, further investigation of prison policy and functionality is necessary to address the gap in HCV treatment initiation. Moreover, screening requirements for HCV treatment at the clinical level need to be addressed. These findings will improve our understanding of healthcare barriers in prisons, mitigating treatment delay to achieve HCV global elimination.
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1859-A | THE RISK OF HEPATOCELLULAR CARCINOMA DEPENDING ON LIVER CIRRHOSIS IN PATIENTS WITH CHRONIC HEPATITIS C: A NATIONAL COHORT STUDY

Jong-In Chang[1], Gi Hyeon Seo[2], Eunju Kim[1], Young Youn Cho[1] and Hyung Joon Kim[1], (1)Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea, (2)Health Insurance Review and Assessment of Service, Seoul, Korea

Background: Current direct-acting antiviral (DAA) treatments for the hepatitis C virus achieve high rates of sustained virological response, thus improving clinical outcomes. Chronic hepatitis C patients are at-risk for hepatocellular carcinoma (HCC) even after DAA treatment. Limited national data exist on the long-term clinical course of DAA use and whether surveillance is needed depending on liver cirrhosis in Korean patients with chronic hepatitis C. **Methods:** This is a population-based retrospective cohort study using the database of the Health Insurance Review and Assessment Service in Korea. A total of 16,344 adult patients who were newly administered Ledipasvir/sofosbuvir or Glecaprevir/pibrentasvir between 2016 and 2021 without a previous history of HCC were included in the analysis. The primary outcome was the incidence of HCC after DAA treatment in patients with and without cirrhosis. The secondary outcome was whether there were differences in HCC incidence by gender and age group. **Results:** The average age of 16,344 patients was 59.4 years, males were 46.9%, the average follow-up period was 23.5 months, and 2,928 (17.9%) patients had liver cirrhosis. The incidence of HCC per 1,000 patient-years was 9.38 in all patients, 3.68 in non-cirrhotic patients, and 33.17 in cirrhotic patients. In both patients with and without cirrhosis, age ≥ 65 and male gender were associated with the incidence of HCC in each subgroup. **Conclusion:** Even after DAA treatment, the risk of HCC remains high in patients with chronic hepatitis C with cirrhosis, whereas the risk is significantly lower in patients without cirrhosis. These results may support the argument that DAA treatment is important before cirrhosis in patients with chronic hepatitis C and that HCC surveillance is necessary continuously after DAA treatment in patients with cirrhosis.
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1860-A | ADDITION OF NEUTROPHIL-TO-LYMPHOCYTE RATIO TO PRE-DAA FIB-4 TO PREDICT DE NOVO LIVER COMPLICATIONS IN HEPATITIS C

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Background: Direct-acting antiviral agents (DAAs) can achieve high sustained virologic response (SVR) in chronic hepatitis C (CHC) patients; yet a proportion of patients still experience de novo liver complications even after SVR. Identification of risk factors is clinically important. FIB-4 index is a useful noninvasive tool to assess fibrosis, while neutrophil-to-lymphocyte ratio (NLR) is a biomarker for systemic inflammation. Our study tried to investigate that whether the addition of

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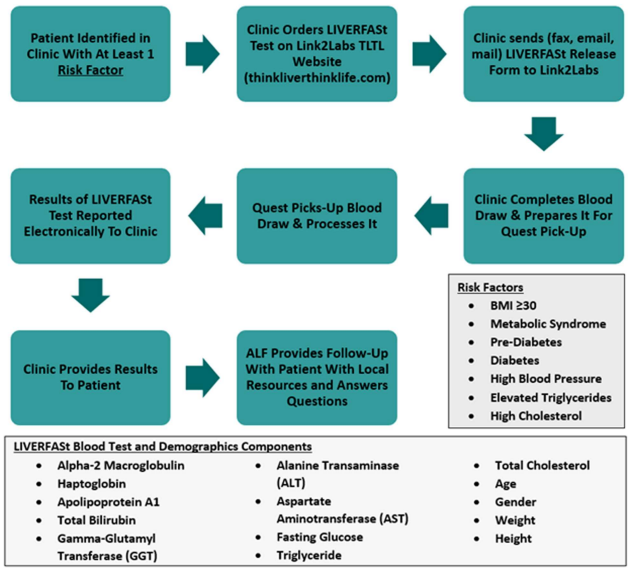
Background: Nonalcoholic fatty liver disease (NAFLD) prevalence is estimated to be 80-100 million in the US. NAFLD is highly under-diagnosed due to inadequate screening programs, and as a result can progress to non-alcoholic steatohepatitis (NASH), liver cirrhosis, liver cancer, the need for liver transplantation, and death. NAFLD is often asymptomatic and disproportionately affects disadvantaged communities. Although early detection allows for timely intervention to improve disease course, screening for fatty liver diseases is not offered as part of routine medical care outside of hepatology clinics. To address this gap, the American Liver Foundation (ALF) launched a pilot NAFLD Screening Program for high-risk individual's in Texas. **Methods:** ALF consulted with public health professionals in Houston to identify a non-profit community-based clinic (Fundación Latinoamericana De Acción Social) providing essential healthcare services to those with limited access. The clinic completed steps necessary to become a screening site to conduct LIVERFASt tests, a blood test that measures 10 biomarkers for liver health (Figure 1). Clinic staff were trained, screening tests were performed on at-risk individual's (Figure 1), and results were analyzed for evidence of steatosis and fibrosis. **Results:** A total of 448 individual's participated in the NAFLD screening program (62% females, mean age = 43 y), among whom 63% had a steatosis score of S1 or higher, with moderate to severe steatosis (S2-S3) in 32%. Importantly, most participants with S2-S3 had little evidence of fibrosis, signaling an opportunity to potentially halt or reverse disease. Participants with scores ≥ S1 were given educational resources on NAFLD and healthy lifestyle choices and linked to healthcare providers for follow-up care. After the pilot program concluded in 2021, the established processes were sustained to continue screening at the clinic. Based on lessons learned, ALF has expanded screening through ALF's National Public Health Campaign, *Think Liver Think Life*, in Federally Qualified Health Centers and Community Clinics in 21 states. **Conclusion:** NAFLD/NASH is an emerging under-diagnosed healthcare crisis, and our pilot program demonstrates the feasibility of widespread screening in high-risk individual's. The ALF plans to expand the *Think Liver Think Life* campaign to all 50 states within 5 years, with the goal to improve education, early diagnosis, and access to care for people with liver disease.

Figure 1: Fatty Liver Disease Screening Project's Clinic Workflow



Disclosures: Robert J. Wong – Gilead Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Exact Sciences: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Thera Technologies: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bausch Health: Consultant, No, No; Salix Pharmaceuticals: Consultant, No, No;
The following people have nothing to disclose: Helene Jordan, Manisha Verma
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2004-A | Agile3+ AND Agile4: TWO DIAGNOSTIC SCORES THAT SYNERGIZE FOR THE PROGNOSTIC ASSESSMENT IN NAFLD

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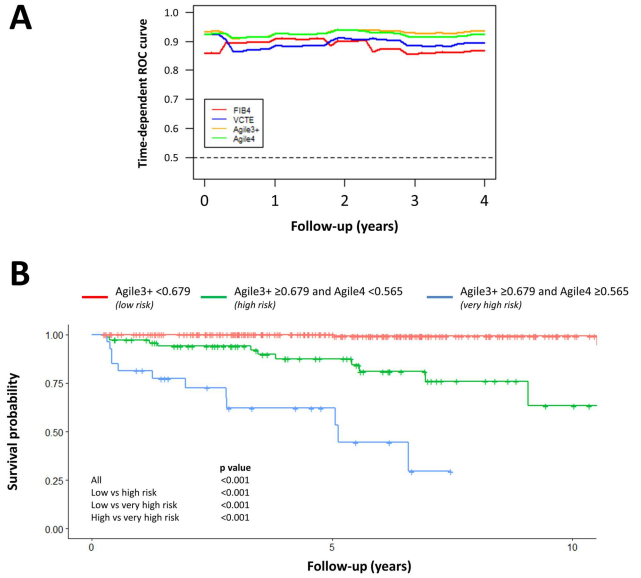
Background: Agile3+ and Agile4 are two elastography-based tests respectively designed for the non-invasive diagnosis of advanced fibrosis and cirrhosis in NAFLD. We aimed to evaluate whether these two tests designed for different diagnostic targets synergize for the prediction of liver-related events (LRE) in NAFLD. **Methods:** This retrospective study included adults with NAFLD from a tertiary care center. The main study outcome was LRE, a composite endpoint combining cirrhosis complication or hepatocellular carcinoma. All patients had FIB4, vibration-controlled transient elastography (VCTE) with FibroScan device, Agile3+ and Agile4 available at baseline. Each non-invasive test stratified patients in three risk groups (low-risk, intermediate risk, high-risk) according to their published thresholds: <1.30 and >2.67 for FIB4; <10 kPa and >15 kPa for VCTE; <0.451 and ≥ 0.679 for Agile3+; <0.251 and ≥ 0.565 for Agile4. **Results:** 341 patients were included (median age: 58 y, male sex: 65%, diabetes: 36%). The rate of patients included in the low / intermediate / high-risk groups with FIB4, VCTE, Agile3+ and Agile4 were, respectively: 43%/46%/11%, 57%/23%/20%, 56%/15%/29%, and 83%/9%/8%. LRE occurred in 27 (8%) patients after a median follow-up of 5.2 years (IQR: 2.9-7.2). Agile3+ and Agile4 provided higher time-dependent ROC curves than VCTE or FIB4 for LRE prediction (Panel A). Most of the patients who experienced LRE during the follow-up were included in the high-risk group with Agile3+ (23 of 27 patients, 85%), versus only 10 (37%) in the high-risk FIB4 group, 15 (56%) in the high-risk VCTE group, and 12 (44%) in the high-risk Agile4 group. Because Agile3+ and Agile4 can be calculated at the same time, we evaluated a stratification based on their combination: low-risk group (Agile3+ <0.679), high-risk group (Agile3+ ≥ 0.679 and Agile4 <0.565), and very high-risk group (Agile3+ ≥ 0.679 and Agile4 ≥ 0.565). Rate of patients included in these three groups were respectively 71%, 21% and 8%. LRE occurred in 4 patients (1.7%) from the low-risk group, 11 patients (15%) from the high-risk group, and 12 patients (44%) from the very high-risk group. Therefore, the Agile3+/Agile4 combination provided the best risk stratification, with Agile4 splitting the Agile3+ high-risk group in two high-risk and very-high groups (Panel B). **Conclusion:** Agile3+ and Agile4, two elastography-based noninvasive tests respectively designed for the diagnosis of advanced fibrosis and cirrhosis, both synergize for a better stratification of the liver-related risk in NAFLD.



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Arun Sanyal – Durect: Stock – privately held company (individual stocks and stock options), No, No; GenFit: Stock – privately held company (individual stocks and stock options), No, No; Gilead: Consultant, No, No; Novartis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genetech: Consultant, No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Path-AI: Consultant, No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be

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2005-A | AI-ASSISTED GUBRA HISTOPATHOLOGICAL OBJECTIVE SCORING TECHNIQUE (GHOST) FOR UNBIASED, FAST AND ACCURATE ASSESSMENT OF DISEASE SEVERITY IN RODENT MODELS OF NASH

Anitta Kinga Sarvari[1], Susanne E. Pors[1], Jacob Nøhr-Meldgaard[1], Casper Salinas[1], Denise Oró Bozzini[1], Henrik B. Hansen[1] and Michael Feigh[2], (1)Gubra, (2) Gubra Aps

Background: Efficacy studies in animal models of non-alcoholic steatohepatitis (NASH) include histopathological endpoints. Clinical-derived NAFLD Activity Scoring (NAS) and Fibrosis Staging system, outlined by Kleiner et al., is reproducible in preclinical models of NASH. Manual histopathological scoring is prone to observer variability which can influence robustness and reproducibility of study results. To enable objective and unbiased histopathological assessment in liver biopsies, we developed GHOST, an deep learning-based digital imaging analysis pipeline for automated NAS and fibrosis scoring. **Methods:** Liver biopsies were obtained from two NASH rodent models, GAN diet-induced obese (GAN DIO-NASH) mouse and choline-deficient L-amino acid-defined high-fat diet (CDAA-HFD) rat. Age-matched chow-fed mice and rats served as normal controls. Automated GHOST deep learning computational analysis of NAS and fibrosis scores was performed on hematoxylin-eosin (HE) and picrosirius red (PSR) stained sections. GHOST module was extended to enable automated analysis of fibrosis severity in CDAA-HFD rats using the Ishak fibrosis scoring system. All GHOST data were validated by manual scoring by expert histopathologists. Quantitative morphometrics, derived from scoring variables, includeddensity of hepatocytes with lipid droplets, number of inflammatory foci, and %-area of fibrosis. **Results:** GHOST accurately and reproducibly detected hepatic central veins and portal areas in GAN DIO-NASH mice and CDAA-HFD rats , enabling segmentation of zones for clinical histopathological scoring. In HE stained sections, hepatocytes, inflammatory cells, and ballooned hepatocytes were identified. Inflammatory foci were considered as clusters of ≥ 4 inflammatory cells. NAS was computed and validated using 338 mouse liver biopsies with a Cohen´s Kappa value of 0.72, indicating agreement between AI-assisted and manual scoring of NAS. PSR-stained collagen fibers were localized in the sinusoidal and periportal space by GHOST, identifying collagen forming bridges and branch points. Kleiner fibrosis stage was computed and validated using 537 mouse liver biopsies, achieving

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The following people have nothing to disclose: Kanji Yamaguchi, Toshihide Shima, Yasuhide Mitsumoto, Takeshi Okanoue

2010-A | ARTIFICIAL INTELLIGENCE-BASED MEASUREMENT OF NON-ALCOHOLIC STEATOHEPATITIS (AIM-NASH) IMPROVES INDIVIDUAL PATHOLOGISTS ACCURACY AND DECREASES INTER-PATHOLOGIST VARIABILITY IN NASH ASSESSMENT

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

Pinnacle Clinical Research Center, San Antonio, TX, (12)Sorbonne Université, Assistance Publique-Hôpitaux De Paris, Hôpital Pitié Salpêtrière, Institute of Cardiometabolism and Nutrition (ICAN)

Background: Histologic scoring systems for NASH have suboptimal inter-reader agreement, even amongst expert hepatopathologists (HPs). Misclassification of NAFLD activity and fibrosis staging impacts NASH clinical trial enrollment and endpoint assessment with inaccurate and imprecise measurement of histologic change over time. High variability limits comparison of results between clinical trial phases and between drug classes. In this study, AIM-NASH (PathAI) was evaluated for accuracy alone and for use as an assistive tool to HPs in assessment of liver biopsies in a NASH clinical trial population. **Methods:** In a clinical validation (CV) study1, de-identified biopsy samples representing cirrhotic and non-cirrhotic subjects were collected from multiple Phase II and Phase III NASH trials. A panel of expert HPs established ground truth (GT) NASH scores. Cases were also digitally evaluated by at least 3 other experienced HPs who independently provided NAS activity grades and CRN fibrosis stage. After a minimum 2-week washout period, individual HPs AI-assisted scores were collected. Accuracy of AIM-NASH alone and HP's manual reads was assessed for the full CV population against GT. Accuracy and inter-reader agreement was assessed with and without AI-assistance, and was performed on a subset of cases where either (a) cases where the same HP read with and without AI-assistance (ranging from 86-216 samples per HP or (b) cases were scored with AI-assistance by multiple HPs (ranging from 10 to 83 slides; Table 1). **Results:** AIM-NASH alone demonstrated superior accuracy to HPs for hepatocellular ballooning and lobular inflammation (weighted kappa [WK] differences of 0.119 and 0.148; both $p < 0.0001$) and non-inferior accuracy for steatosis and fibrosis (WK differences of 0.002; [$p < 0.0001$] and -0.009; [$p < 0.001$]). AI-assistance improved HPs' accuracy for lobular inflammation and hepatocellular ballooning (WK difference of 0.088, and 0.11, respectively), while HPs' accuracy for fibrosis and steatosis compared to GT were largely unchanged with AI-assistance (WK difference of 0.012 and 0.000). AI-assistance decreased inter-pathologist variability for all features with a WK difference ranging in 0.314-0.771. Inter-reader agreements with AI-assistance were higher than published literature for all features (Table 1). **Conclusion:** AIM-NASH is an accurate tool for NASH assessment for all histologic features. In a subanalysis where the same readers performed assisted and manual reads, AI-assisted HPs displayed improved accuracy for assessment of lobular inflammation and hepatocellular ballooning and showed higher inter-reader agreement for all features. These data show that AIM-NASH may help to standardize histologic scoring by increasing accuracy and reducing inter-reader variability in those features most difficult to score in clinical trial populations, allowing for a more reliable assessment of therapeutics under development.

Table 1: Inter-pathologist agreement rates with and without AI (for cases with >10 reads for comparison)

Histologic Feature	Mean WK Inter-reader agreement with AI assistance (range)	Mean Inter-reader agreement without AI assistance (range)	Average Inter-reader WK from literature[2]
Steatosis	0.986 (0.958-1)	0.672 (0.503-0.734)	0.609
Lobular Inflammation	1	0.229 (-0.047-0.466)	0.328
Hepatocellular Ballooning	0.995 (0.973 - 1)	0.383 (0.281-0.448)	0.517
Fibrosis	0.958 (0.906 - 1)	0.493(0.091-0.735)	0.484

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2015-A | AT-RISK NASH IDENTIFICATION USING AN ALGORITHM THAT COMBINES FIB-4 + MASEF (METABOLOMICS-ADVANCED STEATOHEPATITIS FIBROSIS SCORE)

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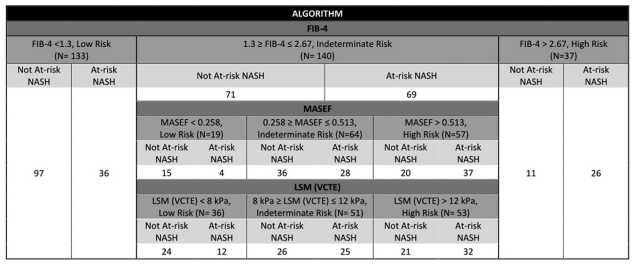
Background: Early identification of those with NAFLD activity score ≥ 4 (with at least 1 for steatosis, lobular inflammation, and ballooning) and significant fibrosis or "at-risk NASH" is a priority as these patients are at increased risk for disease progression and may benefit from therapies. Here we aim to study whether the MASEF score could be used alternatively to liver stiffness measurements (LSM) by transient elastography (VCTE) in the FIB-4+LSM by VCTE algorithm that is currently recommended by several guidance publications. **Methods:** This study included 310 participants that had undergone liver biopsy, LSM by VCT and MASEF score analysis. MASEF score is a highly specific metabolomics-driven score to identify at-risk NASH based on 12 lipids, body mass index, aspartate aminotransferase and alanine aminotransferase. We compared the performance of a FIB-4+MASEF algorithm to that of FIB-4+LSM by VCTE. **Results:** 133 (43%) of 310 patients had FIB-4 < 1.30 and were classified as low risk of having at-risk NASH, 37 (12%) of 310 patients had FIB-4 > 2.67 and were classified as high risk, and 140 (45%) of 310 were classified into the indeterminate or grey zone and then were further analyzed by MASEF score or LSM by VCTE. When using MASEF as the second test after FIB-4, 14% of patients had MASEF < 0.258 and were classified as not at-risk NASH, 41% had MASEF > 0.513 and were classified as at-risk NASH, and 45% fell into the indeterminate zone. Among patients with MASEF < 0.258, 79% were correctly classified and only 4 (21%) were misclassified (NAS ≥ 4 with ≥F2). Among patients with MASEF > 0.513, 37 (65%) were correctly classified, and 20 (35%) were misclassified. When using LSM by VCTE as the second test after FIB-4, 25% of patients had LSM < 8 kPa and were classified as not at-risk NASH, 38% had LSM > 12 kPa and were classified as at-risk NASH, and 36% fell into the grey zone. Among patients with LSM < 8 kPa, 67% were correctly classified and 12 (33%) were misclassified. Among patients with LSM > 12 kPa, 32 (60%) were correctly classified, and 21 (39%) were misclassified. Complete classifications are shown in the table. The overall performance of both algorithms when using MASEF score or LSM by VCTE as the second test after FIB-4 did not show significant differences (p = 0.69). **Conclusion:** MASEF is a promising diagnostic tool for the assessment of at-risk NASH that can be used alternatively to LSM by VCTE in the FIB-4+LSM by VCTE algorithm that is currently recommended by the AGA and EASL.



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2016-A | AUTOMATED AI-BASED MORPHOMETRIC ANALYSIS OF FIBROSIS REVEALS SIGNIFICANT FIBROSIS CHANGES IN T2DM VS NON-T2DM NASH PATIENTS WITH ADVANCED FIBROSIS

Cindy Serdjebi, Bastien Lepoivre, Florine Chandes and Yvon Jule, Biocellvia

Background: Non-alcoholic steatohepatitis (NASH) is the most severe form of fatty liver diseases. Type 2 diabetes mellitus (T2DM) is known as a major risk factor for fibrosis development, and drugs currently under development in NASH address both heath issues, with no drug approved so far. Knowing T2DM patients are at high-risk of severe fibrosis, we have compared fibrosis stages and characteristics of NASH patients according their T2DM status using MorphoQuant, a fully-automated user-independent morphometric software. **Methods:** 107 patients were enrolled in this study. Both untreated and treated patients for T2DM were considered as T2DM patients. Liver biopsies were scored by a blinded expert pathologist according to the NASH CRN for steatosis, inflammation, ballooning and fibrosis. Patients were considered NASH if NAS $\geq$ 4. For MorphoQuant™ analysis, picrosirius red (PSR)-stained slides were prepared and scanned at X20 magnification. Steatosis, vesicle size, total collagen, periductular, perisinusoidal, perivascular and septal collagens, as well as collagen fiber width and length were assessed. TD2M and non-T2DM patients were compared for all readouts using a Mann-Whitney test. **Results:** Among the 107 patients, 53 patients had T2DM. Neither difference was seen in fibrosis stage distribution between T2DM and not-T2DM NASH patients, nor for steatosis, inflammation, and ballooning grades. When overall comparing TD2M versus non-T2DM NASH patients according to their fibrosis stage, nond ifference was seen for fibrosis-related endpoints and steatosis. Interestingly, in NASH patients with F3 stage, TD2M patients had significantly less steatosis, and more fibrosis, expressed as collagen content (p-values = 0.0075 and 0.0164, respectively). When looking at fibrosis distribution and features, TD2M patients had more perivascular and septal collagen than non-T2DM patients (p-values = 0.0145 and 0.006, respectively), their mean septa length was longer (0.036), as well as their maximal septa length and width (0.035 and 0.028). No changed was observed for perisinusoidal fibrosis, or for F1-F2 NASH patients. **Conclusion:** F3 T2DM NASH patients display significantly different features from F3 non-T2DM patients. These differences could be only captured using morphometric digital analysis of NASH and fibrosis features. Particularly, fibrosis was more developed and differently distributed between non-T2DM and T2DM patients. Such findings are in alignment with longer history of liver injury and more advanced fibrosis in T2DM patients and show the limitations of using scores for patient's risk stratification.
Disclosures: Cindy Serdjebi – Biocellvia: Employee, Yes, No; Biocellvia: Stock – privately held company (individual stocks and stock options), Yes, No;
Bastien Lepoivre – Biocellvia: Employee, Yes, No; Biocellvia: Stock – privately held company (individual stocks and stock options), Yes, No;
Florine Chandes – Biocellvia: Employee, Yes, No;
Yvon Jule – Biocellvia: Stock – privately held company (individual stocks and stock options), Yes, No;

2017-A | BMI50+-FIBROSIS SCORE – A NEW NON-INVASIVE TEST FOR LIVER FIBROSIS IN PATIENTS WITH OBESITY AND A BMI > 50 KG/m²

Maximilian Joseph Brol[1], Uta Drebber[2], Xiaojie Yu[2], Robert Schierwagen[1], Sabine Klein[1], Andreas Plamper[3], Margarete Odenthal[2], Wenyi Gu[1], Frank Erhard Uschner[1], Karl Peter Rheinwalt[3] and Jonel Trebicka[1,4], (1)University Hospital Münster, (2) University Hospital of Cologne, (3)St. Franziskus-Hospital Cologne, (4)European Foundation for the Study of Chronic Liver Failure and Grifols Chair, Barcelona, Spain

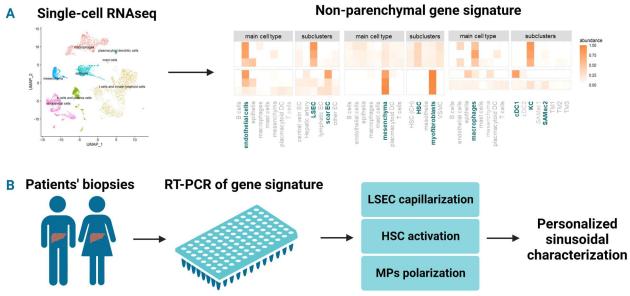
Background: Liver fibrosis is a hallmark of chronic liver disease. Especially in non-alcoholic fatty liver disease (NAFLD), awareness of liver fibrosis is key for patient stratification and planning of follow-up care. Current non-invasive tests (NIT) for liver fibrosis show poor performance in patients with obesity and to date no NIT

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

2020-A | CHARACTERIZATION OF RELEVANT HEPATIC SINUSOIDAL CELL POPULATIONS IN HUMAN CHRONIC LIVER DISEASE: FROM SINGLE-CELL DATA TO PERSONALIZED MEDICINE

Sergi Guixé-Muntet[1], Anabel Fernandez-Iglesias[1], David Sanfeliu-Redondo[1] and Jordi Gracia-Sancho[1,2], (1)Idibaps - Hospital Clínic Barcelona - Ciberehd, Barcelona, Spain, (2)Inselspital - University of Bern, Bern, Switzerland

Background: Transcriptomic data from hepatic tissue mainly represents the most abundant cell types in the liver and masks smaller cell subpopulations, such as non-parenchymal cells (liver sinusoidal endothelial cells, LSECs; hepatic stellate cells, HSC; and macrophages, MP), with high interest for the study of chronic liver diseases (CLD). Single-cell sequencing allows for finer analyses, but its implementation for routine patient care is nowadays unrealistic. The aim of this study was to propose an unbiased single-cell RNA seq-derived gene panel that could reliably define the state of the liver sinusoid in health and disease. **Methods:** We reanalyzed published data from liver sc-RNAseq and generated signature matrices with specific genes for each of the non-parenchymal cells populations. These matrices were used on our RNAseq data from human livers to estimate the changes in sinusoidal cells subpopulations (healthy vs activated / dedifferentiated populations) in CLD. Validations were performed with standard RT-PCR. **Results:** Gene deconvolution from decompensated cirrhotic livers (ethanol, $n = 12$) showed significant increments in capillarized LSECs ($FC = 5.7$), activated HSC ($FC = 1.8$), and fiber-associated MP ($FC = 4.9$) vs control tissues, which were validated in an external cohort of patients with NASH ($n = 39$, GSE139602). 6 genes per cell type (LSEC, HSC, MP) were chosen as the most specific (95% expression vs other hepatic cell types) and the differential expression of said genes was validated by RT-PCR in an internal cohort ($n = 19$ control, $n = 36$ cirrhosis, $p < 0.05$) and in an external cohort of 216 patients with NAFLD-NASH (GSE135251) with different METAVIR stages (control, NAFLD and NASH F0 to F4). Importantly, our panel was able to discriminate samples from early vs advanced CLD patients with an accuracy of 96% and 80%, respectively, and predicted endothelial capillarization ($r = 0.90$, $p < 0.001$), HSC activation ($r = 0.77$, $p < 0.001$) and macrophage polarization ($r = 0.79$, $p < 0.001$). **Conclusion:** This unbiassed gene panel, resulting from an advanced re-analysis of available data, can be easily assessed by accessible techniques (RT-PCR) and allows the characterization of sinusoidal cells phenotype in human liver tissue. This gene signature could be a useful tool for personalized clinical decision making, aiding in the diagnosis, assessment of drug response or in choosing the most relevant cell target for therapy for an individual patient.



Graphical abstract. A) From single-cell RNAseq data we obtained a gene signature that defines the non-parenchymal phenotype in chronic liver disease. B) This specific gene signature was able to identify phenotypical alterations in each sinusoidal cell population in human liver biopsies, providing highly accurated diagnosis.

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The following people have nothing to disclose: Anabel Fernandez-Iglesias, David Sanfeliu-Redondo
Disclosure information not available at the time of publication: Sergi Guixé-Muntet

2021-A | CHARACTERIZING SKELETAL MUSCLE COMPOSITION AND FUNCTION IN PATIENTS WITH CHRONIC LIVER DISEASE

Domenico Chavez[1], Umai Giraldo[1], Geneva Roche[1], Mikael Fredrik Forsgren[2,3], Mohammad S. Siddiqui[1] and Danielle Kirkman[1], (1)Virginia Commonwealth University, (2)Linköping University, (3)Amra Medical

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

Background: Skeletal muscle (SM) dystrophy and myosteatosis are emerging as hallmark manifestations of chronic liver disease (CLD). These alterations in body composition could have marked implications for functional status that would render these patients vulnerable to physiological stressors. The aim of this study was to characterize SM quantity, quality and function in patients with CLD. **Methods:** In this prospective cohort study, 21 patients with CLD (Age 57 ± 11; Female 76%: Black 14%) underwent an 8-minute full-body 3.0 T MRI to provide a comprehensive and quantitative SM composition analysis using AMRA® Researcher. SM quality was determined by isometric knee extensor strength assessed by dynamometry. A battery of physical function tests was performed to assess speed and agility, lower body functional strength and aerobic capacity. Frailty status was determined according to the Fried criteria. Participants also completed an assessment of mitochondrial oxidative capacity of the wrist flexor muscle group. Near infrared spectroscopy coupled with repeated, transient arterial occlusions were used to measure the recovery kinetics of oxygen consumption following a bout of hand grip exercise. The post-exercise metabolic recovery rate constant (T_c) was calculated and reported as an index of mitochondrial plasticity. **Results:** Patients with lower muscle mass had reduced knee extensor strength ($r = 0.50$, $p < 0.05$), worse functional agility ($r = 0.58$, $p < 0.01$) and impaired lower body functional strength ($r = 0.61$, $p < 0.01$). Patients with higher muscle fat infiltration (MFI) had reduced knee extensor strength ($r = -0.70$, $p < 0.01$), worse functional agility ($r = -0.64$, $p < 0.01$), impaired lower body functional strength ($r = -0.44$, $p < 0.01$) and lower aerobic capacity ($r = -0.74$, $p < 0.01$). Frail patients had significantly higher mean MFI (8.9 ± 1.2%) compared to pre-frail patients (6.4 ± 0.5%; $p < 0.05$). This cohort of patients with CLD had significantly diminished SM mitochondrial oxidative capacity (T_c: 75 ± 7 s) compared to healthy controls (52 ± 4 s; $p < 0.05$) indicating diminished SM mitochondrial function. **Conclusion:** These findings provide foundational data demonstrating the association between muscle composition (quantity and quality) and functional status in patients with CLD. Moreover, patients demonstrate worse SM mitochondrial plasticity compared to their healthy counterparts. These findings could facilitate the development of biologically relevant biomarkers, risk stratification and therapeutic options.

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Disclosure information not available at the time of publication: Umai Giraldo, Geneva Roche, Danielle Kirkman

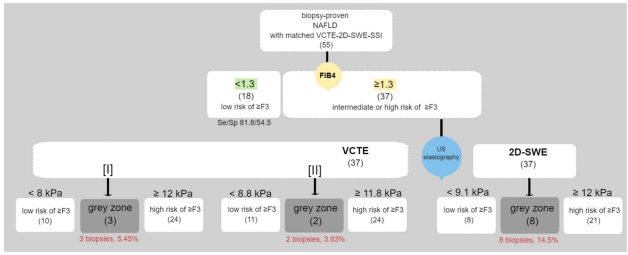
2022-A | CHKA AND MBOAT7 AS POTENTIAL TARGETS FOR MAFLD-HCC WITH EARLY STAGE OF FIBROSIS: REVEALED BY METABOLOMICS AND TRANSCRIPTOMIC ANALYSIS

Jihan Sun[1], Fatima Dahboul[1], Estelle Pujos-Guillot[2], Stéphanie Durand[2], Mélanie Petera[2], Delphine Centeno[2], Benoit Colsch[3], Zoulim Guillaume[4], Aicha Demidem[5] and Armando Abergel[6], (1)Université Clermont Auvergne, (2)Inrae-UNH, (3)CEA-Paris Saclay, (4)UNH-1019, (5)UNH, (6)CHU-Clermont Ferrand

Background: Metabolic dysfunction Associated Fatty Liver Disease (MAFLD) is increasingly recognized as a major health burden in developed countries. It can eventually progress to HCC and up to 25% of MAFLD-HCC arise in the absence of severe liver fibrosis, posing a challenge for early detection and treatment (De A et al., 2020, J clin Exp Hepatol). We previously reported the existence of 2 phenotypes of MAFLD-HCC by metabolomics analysis according to fibrosis level (F0F1 *vs.* F3F4) (Buchard et al., 2021, Metabolites, Buchard et al., 2021, AASLD Hepatology). The aim of our current study is to explore lipid pathways and identify potential biomarkers related to MAFLD-HCC. **Methods:** Fifty-six pairs (F0F1 = 28, F3F4 = 28) of human MAFLD-HCC (TT) and non-tumor tissues (NTT) and five healthy tissues were collected from CRB. Foie. A non-targeted metabolomics strategy was applied using LC-MS. Based on the results of LC-MS, qRT-PCR regarding sphingomyelin synthase 2 (SGMS2), sphingomyelin phosphodiesterase 1 (SMPD1), choline Kinase alpha (CHKA) and membrane-bound O-acyltransferase 7 (MBOAT7) was performed. **Results:** Firstly, LC-MS analysis shown that the comparison between the two groups of MAFLD-TT and MAFLD-NTT revealed the presence of two different lipids profiles according to the fibrosis severity (F0F1 *vs.* F3F4). Most of sphingolipids including ceramides (Cer) and sphingomyelins (SM), and glycerophospholipids, including phosphatidylcholine (PC), phosphatidylethanolamine (PE) and phosphatidylinositol (PI) were increased in MAFLD-HCC-F0F1 while they decreased in MAFLD-HCC-F3F4 (Fig. 1A). Secondly, the results of qRT-PCR indicated that the RNA expression of SGMS2, SMPD1 remain unchanged in MAFLD-TT compared with NTT, regardless of fibrosis level. In contrast, the RNA expression of CHKA and MBOAT7 were exclusively up-regulated in MAFLD-TT-F0F1 compared to NTT-F0F1 using healthy tissues as control (Fig. 1B). These results were in accordance with our metabolomics data that have shown that PC content were highly accumulated in

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

prediction of advanced fibrosis (≥ F3) is a crucial aspect in their management. **Methods:** In a retrospective study, we analyzed 149 consecutive patients with biopsy-proven NAFLD/NASH who underwent liver biopsy (LB) at our tertiary medical center between 2013 and 2021. Patients with concurrent HCC or other causes of liver disease were excluded. We assessed the diagnostic accuracy of VCTE (vibration controlled transient elastography using M or XL probes according to the equipment's recommendations, min. 10 valid measurements, reliable) and of 2D-SWE-SSI (two-dimensional shear wave elastography, Aixplorer, SuperSonic Imagine, min. 5 valid measurements, reliable) in detecting different stages of liver fibrosis. A subgroup of patients with baseline matched VCTE-2D-SWE-SSI were further included in comparative two-step algorithms (FIB4+VCTE vs. FIB4+2D-SWE-SSI) to assess the diagnostic performance and the need for LB in unclassified patients for the diagnosis of ≥ F3. **Results:** Out of 149 patients, 2(1.3%) presented F0 on biopsy, 30(20.2%) F1, 42(28.2%) F2, 35(23.5%) F3, 40 (26.8%) F4 according to NASH CRN. The AUC for FIB4 (1.3) in detecting ≥ F3 for all patients was 0.78 (95%CI). 119(95.7%) presented baseline reliable VCTE measurements, 73(93.2%) baseline reliable 2D-SWE-SSI measurements and 55(36.9%) matched VCTE-2D-SWE SSI. The AUCs for VCTE in detecting ≥ F2, ≥ F3 and F4 were 0.889, 0.928, and 0.939 with optimal cut-offs (Youden Index) of 8.8 kPa, 12.2 kPa, and 16.8 kPa. The AUCs for 2D-SWE in detecting ≥ F2, ≥ F3 and F4 were 0.873, 0.908, and 0.882 (95%CI), with optimal cut-offs (Youden Index) of 7.5 kPa, 9.4 kPa, and 12.5 kPa. For better Se and Sp, we considered rule-in and rule-out cut-offs for ≥ F3 with both elastography techniques: for VCTE 8.8 kPa (Se/Sp = 93.85/74.07) and 11.8 kPa (Se/Sp = 81.54/94.44); for 2D-SWE-SSI 9.1 kPa (Se/Sp = 91.89/80.56) and 12 kPa (Se/Sp = 70.27/91.67). Using this thresholds and the 8 and 12 kPa cut-offs for VCTE, the need for LB for the patients in grey zone remained 3(5.45%) for FIB4+VCTE standard cut-offs, 2(3.63%) for FIB4+VCTE our cut-offs and 8 (14.5%) for FIB4+2D-SWE-SSI. No significant differences were observed among strategies (McNemar's exact test). **Conclusion:** Both FIB4+VCTE and FIB4 +2D-SWE exhibit potential as promising screening approaches for predicting ≥ F3 in suspected NAFLD.



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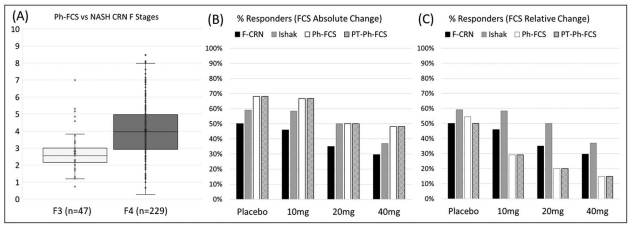
2038-A | DIGITAL PATHOLOGY QUANTITATIVE IMAGE ANALYSIS AND AI METHOD DETECTS THE TREATMENT EFFECT OF PEGBELFERMIN IN CIRRHOSIS PATIENTS WITH A PERFORMANCE THAT BENCHMARKS MANUAL HISTOLOGICAL ASSESSMENT

Li Chen[1], Anne Minnich[2], Edgar D. Charles[2], Zachary D. Goodman[3], Mathieu M. Petitjean[4] and Arun Sanyal[5], (1)Pharmanest, (2)Bristol Myers Squibb, (3)Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, (4)Pharmanest Inc, (5)Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA

Background: Manual histological evaluation of liver biopsy is the gold standard for fibrosis staging in Non-Alcoholic Steatohepatitis (NASH), but it is limited by its inter and intra-reader variability. Digital Pathology image analysis (FibroNest™) has the potential to overcome the current limitation of such standards. This exploratory post-hoc analysis compared FibroNest's continuous scores with NASH-CRN categorical stages in patients with NASH from the phase 2b FALCON2 study (NTC03486912). **Methods:** Eligible adults were 18-75 years of age (N = 145) with NASH diagnosed by histologic assessment of liver biopsy according to NASH CRN criteria and stage 4 fibrosis, defined as Cirrhosis. During the 48-week double-blind treatment period, patients received 10mg, 20mg, or 40mg pegbelfermin subcutaneous or placebo once weekly. Liver biopsies were obtained six months before or during screening and at week 48. Formalin-fixed, paraffin embedded sections of the liver biopsies were stained with Masson Trichrome and imaged at 40X. Quantitative image analysis was performed to extract single-fiber quantitative traits (qFTs, N = 315) from the fibrosis histological phenotype. A previously validated selection of principal qFTs were normalized and combined into a fibrosis severity score (Ph-FCS, 1 to 10). A prospective score (PT-Ph-FCS) was developed to normalize the Ph-FCS on non-steatotic parenchymal tissue. Each digital image was evaluated for quality along 20 dimensions (tissue processing, staining, scanning) to generate a Digital Biopsy Adequacy score (DBA). **Results:** Ph-FCS was able to classify F3 (n = 47) from F4 (n = 229) stages with a sensitivity (specificity) of 73.80% (74.47%) for a Ph-CFS = 3 cut off value (Fig. A). Groups sizes with paired biopsies were

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

22, 24, 20, 27 for the placebo,10mg, 20mg, 40mg groups following removal of images considered non-evaluable for FibroNest algorithms (i.e., DBA < 5). Responders were identified with a 1-unit reduction for the histological stage (Fig. B-C). Using an absolute reduction of 0.3 (4-fold higher than the analytical variability), the Ph-FCS resolved 15% to 20% (resp. 0% to 10%) more responders than NASH CRN (resp. Ishak) categorical stages which is consistent with an increased detection threshold (Fig. B). A 25% relative reduction of Ph-FCS (corresponding to an absolute change of 0.75 to 2 for 3 < Ph-FCS < 8) detected fewer responders than when using NASH-CRN or Ishrak (Fig. C). There was no difference between the Ph-FCS and the PT-Ph-FCS which is attributed to the lack of antisteatotic effect of the treatment in this study, as reported elsewhere. **Conclusion:** Quantitative digital pathology image analysis and AI generates continuous scores for fibrosis that enhance conventional histological staging and resolve the continuum of cirrhosis. The definition of meaningful change criteria using this continuous scoring remains to be improved.



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Anne Minnich – Bristol Myers Squibb: Consultant, No, No;
Edgar D. Charles – Bristol Myers Squibb: Employee, Yes, No; Bristol Myers Squibb: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No;
Arun Sanyal – Durect: Stock – privately held company (individual stocks and stock options), No, No; GenFit: Stock – privately held company (individual stocks and stock options), No, No; Gilead: Consultant, No, No; Novartis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genetech: Consultant, No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Path-AI: Consultant, No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Histoindex: Consultant, No, No; Fibronest: Consultant, No, No; Hemoshear: Stock – privately held company (individual stocks and stock options), No, No; Hemoshear: Consultant, No, No; Inversago: Stock – privately held company (individual stocks and stock options), No, No; Biocellvia: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Eli Lilly: Consultant, No, No; Novo Nordisk: Consultant, No, No; Boehringer Ingelheim: Consultant, No, No; Astra Zeneca: Consultant, No, No; Boehringer Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Akero: Consultant, No, No; Intercept: Consultant, No, No; Fractyl: Consultant, No, No; Madrigal: Consultant, No, No; Northsea: Consultant, No, No; Takeda: Consultant, No, No; Regeneron: Consultant, No, No; Eli Lilly: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Alnylam: Consultant, No, No; Novo Nordisk: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Consultant, No, No; Glaxo Smith Kline: Consultant, No, No; Novartis: Consultant, No, No; Tern: Consultant, No, No; Inventiva: Consultant, No, No; Target Pharmasolutions: Consultant, No, No; Tiziana: Stock – privately held company (individual stocks and stock options), No, No; Uptodate: Royalties or patent beneficiary, No, No; Elsevier: Royalties or patent beneficiary, No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bristol Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Astra Zeneca: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
The following people have nothing to disclose: Zachary D. Goodman, Mathieu M. Petitjean

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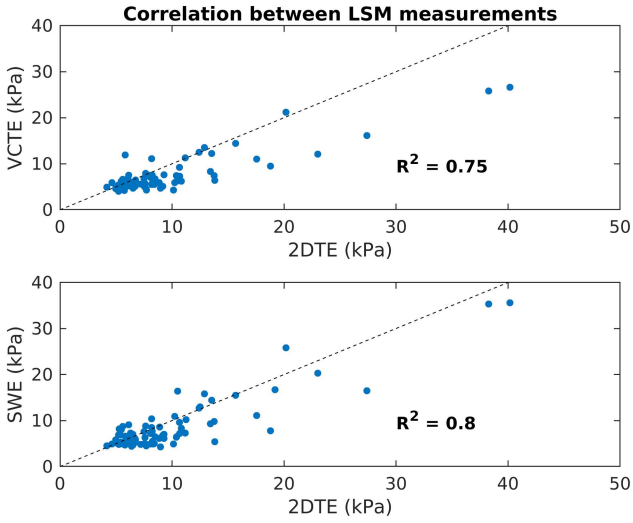
Correlation graphs between LSM obtained from 2DTE on Hepatoscope and FS VCTE (top) or Aixplorer SWE (bottom).



Disclosures: Victor De Ledinghen – E-Scopics: Consultant, Yes, No;
Adrien Besson – E-Scopics: Employee, Yes, No;
Joel Gay – E-Scopics: Employee, Yes, No;
Claude Cohen-Bacrie – E-Scopics: Executive role , Yes, No;
The following people have nothing to disclose: Dan Cohen-Dutartre, Francoise Manon, Joelle Abiven, Anne-Laure De Araujo, Rhizlane Houmadi, Julie Dupuy, Juliette Foucher

◆ 2067-A | LIVER STIFFNESS PROGRESSION IN BIOPSY-PROVEN NONALCOHOLIC FATTY LIVER DISEASE AMONG PEOPLE WITH DIABETES VERSUS PEOPLE WITHOUT DIABETES: A MULTICENTER STUDY

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Background: There are limited data regarding whether liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) progresses faster in people with type 2 diabetes mellitus (T2DM) versus those without T2DM in biopsy-proven nonalcoholic fatty liver disease (NAFLD). Therefore, we aimed to examine the time-to-progression of LSM between participants with versus without T2DM who had available paired VCTEs in a large, multicenter, multiethnic cohort study within the NASH CRN. **Methods:** This study included adult participants with biopsy-proven NAFLD who had VCTEs at least one year apart, recruited at eight sites across the United States as part of the NIDDK-sponsored NASH CRN. The Cox proportional hazards model was used to evaluate the hazards ratio (HR) for LSM progression and regression, defined by an upward or downward change, respectively, in the Baveno VII LSM categories for compensated advanced chronic liver disease (<10 kPa, 10-14.9 kPa, 15.0-19.9 kPa, 20.0-24.9 kPa, ≥ 25.0 kPa), compared between T2DM versus non-T2DM at baseline. **Results:** This study included 1,340 adult participants with NAFLD (62% female) with more than one VCTE. The mean ($\pm$SD) age and body mass index were 51.9 ($\pm$12.0) years and 33.9 ($\pm$6.6) kg/m^2, respectively. The median (IQR) time between VCTEs was 4.1(2.5-6.5) years. Participants with T2DM (n = 732) had a significantly higher cumulative incidence of LSM progression at 4-years (13% versus 11%), 6-years (25% versus 18%) and 8-years (52% versus 44%) compared to participants without T2DM (n = 608), $P = 0.008$ (Figure 1). Using multivariable Cox proportional hazards model adjusted for age, sex, BMI, and Hispanic ethnicity, the presence of T2DM was associated with statistically and clinically significant faster LSM progression (adjusted HR 1.31, 95% CI 1.00 – 1.71, $P = 0.046$). The association between T2DM and LSM progression remained consistent in sensitivity analyses for the presence of cirrhosis ($P = 0.03$). There was no significant difference in the time to regression between T2DM versus non-T2DM ($P = 0.78$). **Conclusion:** Utilizing serial VCTE data from a multicenter study of participants with biopsy-proven NAFLD and prospectively collected data, we demonstrate that participants with T2DM have a significantly faster time to LSM progression. These data may have important implications for clinical practice and clinical trial design.

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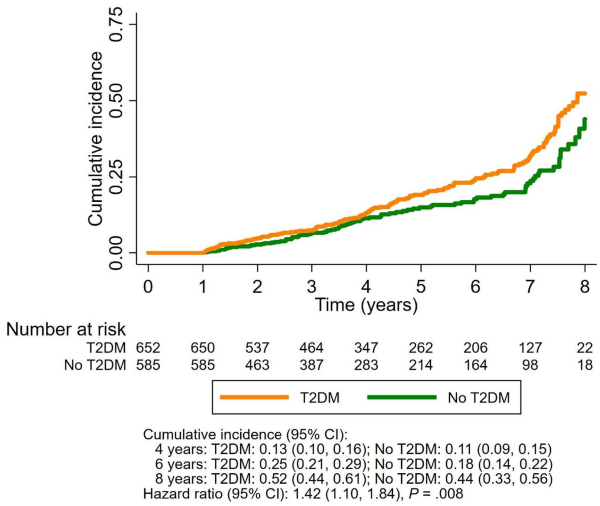
Figure 1. Cumulative incidence of progression of liver stiffness measurement by vibration controlled transient elastography, compared between participants with type 2 diabetes mellitus versus participants without type 2 diabetes mellitus



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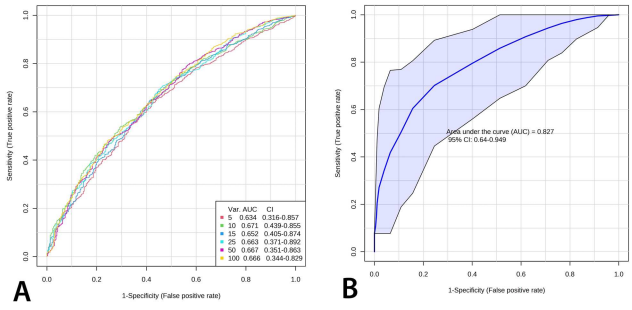
2068-A | LIVER TISSUE PROTEOMICS-BASED PLASMA BIOMARKER FOR NASH

Achuthan Sourianarayanane, Medical College of Wisconsin and Brett Phineey, UC Davis

Background: Diagnosing patients with nonalcoholic steatohepatitis (NASH) among those with nonalcoholic fatty liver disease (NAFLD) is challenging. Liver biopsy and MRI are useful in this regard; however, the former is invasive, while the latter is costly and not readily available. Many plasma-based noninvasive tests have been proposed but have not been effective. This study evaluates the effectiveness of plasma biomarkers based on their correlation with liver tissue proteomics. **Methods:** We included 65 subjects diagnosed with NAFLD (17 without NASH, 38 with NASH but without advanced fibrosis, and 10 with advanced fibrosis) in this study. A portion of liver tissue was flash frozen at the time of liver biopsy and stored at -80°C along with their plasma. Following lipid fraction extraction, the liver tissue was sonicated and digested with trypsin at 37°C. Mass spectrometric analysis was performed for untargeted proteomics of liver tissue and plasma. We used the following parameters to increase the specificity and decrease the number of analytes discovered: q-value < 0.05, log fold change > 2 for liver tissue analysis, and a lesser cut-off of p-value < 0.5 and log fold change > 1 for plasma analysis to detect an adequate number of plasma proteins. **Results:** Among the patients, 20 plasma proteins were found to be up or downregulated between subjects with and without NASH. Plasma proteins were able to differentiate NASH subjects with an area under the receiver operating curve (AUROC) between 0.63 and 0.67 (Figure 1a) by different modeling methods. Among the liver tissue proteins, 66 were up or downregulated between those with and without NASH. None of the 20 plasma proteins of significance were found to be significantly up or downregulated in liver tissue. Of the 20 plasma proteins that were significantly up-or downregulated, only 16 were represented among 3,346 proteins detected by liver tissue proteomic analysis. A biomarker analysis using 16 of the plasma proteins also represented in liver tissue was able to differentiate patients with NASH from those without NASH with an AUROC of 0.827 (Figure 1b). In a model using ten proteins found significant in the liver tissue as a biomarker, patients with NASH were differentiated from those without NASH with an AUROC of 0.955. **Conclusion:** Proteomic analysis of plasma does not correlate with the liver tissue counterpart among subjects with NAFLD. The accuracy of biomarkers based on plasma proteins increases by corroborating proteins of significance with liver tissue analysis. Proteins found to differentiate NASH from NAFLD based on liver tissue analysis and are also represented in plasma would be an ideal noninvasive test to detect NASH.



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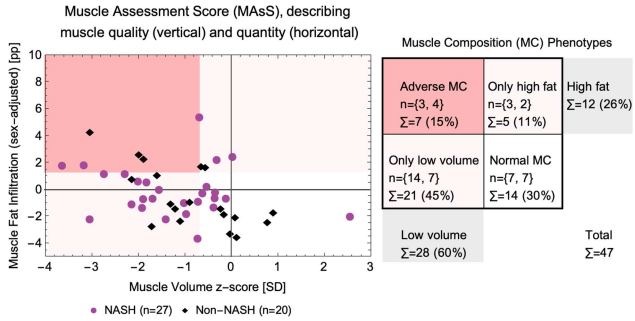
Salman Roghani, Natarajan Ravendhran, Yaron Rotman

2088-A | PATIENTS WITH NASH CIRRHOSIS HAVE SIMILAR MUSCLE COMPOSITION TO NON-NASH PATIENTS ASSESSED BY NOVEL MRI-BASED MUSCLE ASSESSMENT TECHNOLOGY

Omar Jamil[1], Nirmal Desai[2], Jonathan Taylor[1], Carla Harmath[1] and Michael R. Charlton[1], (1)University of Chicago, (2)Loyola University

Background: While frailty and sarcopenia are well recognized markers of mortality and transplant outcomes, the current methods of assessment have limitations and may underestimate sarcopenia in patients with infiltrative muscle fat. MRI the gold standard for body composition analysis. An MRI-based technology to assess muscle health and body composition (AMRA® Profiler 4 MAsS Scan by AMRA Medical) uses a rapid neck-to-knee MRI protocol and automated image analysis technique to measure both muscle fat infiltration and free muscle fat volume and distinguishes between muscle and fat. Comparing muscle composition in patients with cirrhosis secondary to NASH to patients with cirrhosis from other etiologies using MRI has not been reported. **Methods:** A prospective cohort study is being conducted at the University of Chicago and began enrolling patients in August, 2022. Patients with cirrhosis underwent MAsS scan with analysis of muscle fat, muscle volume, subcutaneous fat, visceral fat and liver fat content. The protocol generates age and sex matched muscle fat index and muscle volume index. These indices are combined to create a composite score used to determine muscle composition using both muscle volume and fat infiltration. Patients were divided into two groups, those with cirrhosis secondary to NASH, and those with cirrhosis secondary to other etiologies (Non-NASH). STATA 18 was used for all statistical analyses. **Results:** MAsS Scan has been performed in 47 patients with cirrhosis. 27 patients had cirrhosis secondary to NASH (57%), 8 ETOH (17%), 8 viral (17%), 1 cholestatic (2%) and 3 other (6%). Age (62 and 63.2) and gender (48% female and 40% female) were similar between groups, while the NASH group had significantly more Hispanic (19% to 0%) and White (70% to 30%) patients while the Non-NASH group had more non-Hispanic and Black (55% to 4%) patients. The average BMI of the NASH group (31.2) was statistically higher ($p < 0.05$) than the Non-NASH group (26.9), while the MELD scores were similar (11.1 and 11.5). While the NASH patients had significantly ($p < 0.05$) more visceral fat (5.3L to 3.5L) and liver fat (6.5% to 3.2%), both groups had the same levels of fat infiltrating the thigh muscle (7.9% and 7.9%) and muscle volume (9.5L and 9.5L). As seen in Figure 1, when compared to age and sex matched controls, the muscle fat index and muscle volume index of NASH and Non-NASH patients are similar. The number of patients with adverse muscle composition, or sarcopenia, was 7 (15%) in the total cohort, without a significant difference between the two groups (11% of NASH patients and 20% of Non-NASH). **Conclusion:** Patients with NASH cirrhosis were found to have more visceral fat and liver fat. Visceral fat is correlated with an increased risk of cardiovascular disease. NASH and Non-NASH patients with cirrhosis were found to have similar levels of infiltrative fat and muscle volume as measured by a novel MRI protocol.



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2089-A | PERFORMANCES OF NIS2+TM AND OTHER NON-INVASIVE TESTS FOR THE DETECTION OF AT-RISK NASH ALONG THE BMI SPECTRUM

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Background: Non-alcoholic steatohepatitis (NASH) is a progressive form of non-alcoholic fatty liver disease (NAFLD), the leading cause of chronic liver disease. While obesity is a major risk factor, NAFLD can affect people in all BMI categories. Timely diagnosis of at-risk NASH (NAS ≥ 4 and F ≥ 2), a condition associated with higher risk of liver-related/all-cause mortality, is critical. We compared the performance of NIS2+™, an optimization of the blood-based NIS4® technology for the detection of at-risk NASH, with well-established non-invasive tests (NITs), but designed for fibrosis evaluation, in different BMI-based groups. **Methods:** Among screened patients of the RESOLVE-IT Phase 3 trial (NCT02704403), those with NIS2+™, APRI, ELF™, NFS and FIB4 scores available, and with less than 90 days between liver biopsy and serum samples collection, were selected, resulting in a cohort of N = 2084 patients. This cohort was split in 5 BMI-based groups (lean [n = 84], overweight [n = 514], with obesity Class 1 [n = 727], Class 2 [n = 470] and Class 3 [n = 289]) based on the WHO criteria and according to ethnicity-specific cut-offs. NIS2+™ performance in detecting at-risk NASH in each BMI group was compared to other NITs using AUROC and associated paired Delong tests. Clinical performances (sensitivity, specificity, PPV, NPV) of NIS2+™ in each group using fixed cutoffs for ruling-out/in at-risk NASH were derived. **Results:** The prevalence of at-risk NASH increased with increasing BMI (33.3 to 50.2%, p = 0.0058), driven by a significant increase in NAS scores (3.13 to 4.37, p < 0.0001). ALT and FIB-4, surrogate markers for disease activity and fibrosis respectively, achieved moderate AUROCs for the detection of at-risk NASH (ALT: 0.665-0.755; FIB-4: 0.618-0.688), while NFS yielded the lowest performances in all groups (0.554-0.623). NIS2+™ had the highest accuracy and significantly outperformed all other NITs across the different subpopulations, with AUROCs ranging from 0.784-0.851. NIS2+™ sensitivity when ruling-out and specificity when ruling-in at-risk NASH ranged 0.71-0.96. NIS2+™ sensitivity when ruling-in and specificity when ruling-out at-risk NASH ranged 0.54-0.75. **Conclusion:** Across BMI categories, NIS2+™ significantly achieved the highest performances for the detection of at-risk NASH, returning consistent clinical performances when being used with fixed cutoffs for ruling-out/in at-risk NASH and could thus represent a promising tool to detect at-risk NASH in people at any BMI, including lean people.

Table: AUROC comparison between NITs by BMI group

	NIS2+™	FIB-4		NFS		ELF™		APRI		ALT	
BMI class (kg/m²)	AUROC (95% CI)	AUROC (95% CI)	p value	AUROC (95% CI)	p value	AUROC (95% CI)	p value	AUROC (95% CI)	p value	AUROC (95% CI)	p value
Lean (18.5≤BMI<25)*	**0.851 (0.756, 0.946)**	0.688 (0.554, 0.821)	0.0262	0.591 (0.451, 0.73)	0.0027	0.644 (0.515, 0.774)	0.0057	0.761 (0.64, 0.883)	0.1262	0.706 (0.592, 0.82)	0.0028
Overweight (25≤BMI<30)*	**0.829 (0.793, 0.864)**	0.618 (0.569, 0.667)	<0.0001	0.554 (0.504, 0.604)	<0.0001	0.713 (0.668, 0.758)	<0.0001	0.73 (0.686, 0.773)	<0.0001	0.702 (0.657, 0.747)	<0.0001
Class 1 Obesity (30≤BMI<35)*	**0.784 (0.731, 0.838)**	0.668 (0.628, 0.707)	<0.0001	0.623 (0.583, 0.664)	<0.0001	0.681 (0.642, 0.72)	<0.0001	0.722 (0.685, 0.759)	0.0001	0.665 (0.626, 0.704)	<0.0001
Class 2 Obesity (35≤BMI<40)*	**0.842 (0.806, 0.878)**	0.688 (0.64, 0.736)	<0.0001	0.569 (0.518, 0.621)	<0.0001	0.736 (0.691, 0.781)	<0.0001	0.775 (0.734, 0.817)	0.0001	0.755 (0.712, 0.798)	<0.0001
Class 3 Obesity (BMI≥40)*	**0.829 (0.782, 0.876)**	0.685 (0.624, 0.745)	<0.0001	0.615 (0.55, 0.679)	<0.0001	0.729 (0.672, 0.786)	0.0016	0.746 (0.69, 0.802)	0.0004	0.698 (0.637, 0.758)	<0.0001

* p values have been computed per BMI class by using paired Delong tests, the reference being the NIS2+™ AUROC
* BMI categories adapted for Asian people with Lean (18.5≤BMI<23), Overweight (23≤BMI<25), Class 1 Obesity (25≤BMI<30), Class 2 Obesity (30≤BMI<35) and Class 3 Obesity (BMI≥35)

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as positive, and a confirmatory ELF test was systematically performed. The positive FIB-4 test was confirmed when the second line ELF test was ≥ 9.8 . **Results:** Among the 3427 patients seen in general practice, 869 (25%) had a positive FIB4 score,784 (22.5%) at intermediate (FIB-4:1.3-2.67) and 85 (2.5 %) at high risk of fibrosis (FIB-4 > 2.67). Among the 869 FIB-4 positive patients, 509 (59%) were confirmed by the ELF test. 35% of them were older than 65 years. Confirmation was significantly more frequent in subjects over 65 years of age compared to those under 65 years of age: 84 % vs 16 %, p < 0.0001 and in those with a FIB-4 in the high-risk zone, compared to the intermediate zone: 80% versus 56%, p < 0.0001. For an age-dependent FIB-4 threshold (> 1.3 (< 65 yrs.) /> 2 (> 65 yrs.) which concerned 55% of the FIB-4 positive subjects (n = 481), 56% were confirmed by the ELF test (n = 271). For the FIB-4 threshold of 2, regardless of age which concerned 33% of the FIB-4 positive subjects (n = 284), 74% of the FIB-4 ≥ 2 subjects were confirmed by ELF testing versus 51% of those with a FIB-4 score < 2 (RR 1.88 (95% CI 1.52-2.32) p < 0 .001). The percentage of FIB-4 subjects in the intermediate fibrosis risk decreases from 22.5 % for a FIB-4 between 1.3 and 2.67, to 12 % for a FIB-4 between 1.3/2 and 2.67, and to 6 % for a FIB-4 between 2 and 2.67. **Conclusion:** ELF testing performed in the second line had significantly more confirmed advanced fibrosis in subjects with FIB-4 ≥ 2. A threshold of 2 retains a high percentage of confirmation while reducing the size of the intermediate risk zone for fibrosis and may allow more effective screening for liver fibrosis in primary care.

(1) Ouzan D et al. Prospective screening for significant liver fibrosis by FIB-4 in primary care patients. Eur J Gastroenterol Hepatol 2021;33:986-991. (2) McPherson S. et al. Age as a Confounding Factor for the Diagnosis NAFLD fibrosis Am J Gastroenterol 2017;112:740–51.

FIB-4 confirmation by ELF test according to FIB-4 thresholds

FIB-4 Threshold	N (%)	% confirmation by ELF in subjects with FIB-4 > threshold	% confirmation by ELF in subjects with FIB-4 < threshold
FIB-4>1.3	869 (100%)	509 (59%)	NA
FIB-4 >1.3/2	481 (55%)	271 (56%)	44 %
FIB-4 ≥2	284 (33%)	210 (74%)	51%

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♦ 2100-A | SEQUENTIAL USE OF FIB-4 AND NIS2+™ FOR AN ACCURATE DETECTION OF NON-CIRRHOTIC AT-RISK NASH PATIENTS FOR ENROLLMENT IN NASH CLINICAL TRIALS

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Background: In clinical trials recruiting non-cirrhotic patients with at-risk NASH (NAS ≥ 4; F ≥ 2), many cirrhotic (F4) or non at-risk NASH patients are excluded after undergoing liver biopsy (LB), an invasive and costly procedure. While FIB-4 is a widely used test for fibrosis evaluation, NIS2+™, an optimization of the blood-based NIS4® technology, is designed to robustly identify at-risk NASH and highlighted efficient screening performances for patient referral to LB. We assessed the performance of a sequential use of FIB-4 (for ruling-out F4 patients) followed by NIS2+™ (for ruling-in at-risk NASH) to optimize the screening of NASH trials. **Methods:** Among > 5000 patients that were screened in the RESOLVE-IT Phase 3 trial (NCT02704403), those with non-historical LB, NIS2+™ and FIB-4 available, and ≤ 90 days between LB and serum sample collection were selected, resulting in a cohort of 1929 patients. This cohort was used to compare the screening performance of the RESOLVE-IT trial vs a retrospectively simulated strategy involving FIB-4 followed by NIS2+™. The number of patients needed to screen (NNS), the LB failure rate (LBFR), the screening cost, and the number of F4 referred to LB were estimated for FIB-4 cutoff values of 2.0-3.0, and 0-0.8 for NIS2+™. Performances were estimated for the inclusion of 1000 patients. **Results:** Using the RESOLVE-IT screening process, the LBFR was 60%, with 3220 screenings to include 1000 patients, of which 128 F4 referred to LB and a cost estimated to $15M. An optimal pair of cutoff values (FIB-4 < 2.48, NIS2+™ ≥ 0.53) was derived, to minimize the number of F4 patients wrongly referred to LB while achieving a

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LBFR < 40%, a NNS < 4830 (< 50% increase) and a cost decrease. Using these cutoffs, the sequential use of FIB-4 and NIS2+™ would have reduced the LBFR to 39%, the number of F4 patients referred to LB to 89 (-30%) and the overall cost by $1.1M (-7.3%) with a manageable NNS of 4792. Using NIS2+™ high cutoff (≥ 0.68) following FIB-4 with a cutoff of 2.48 would have further reduced the LBFR (< 31%) and the number of F4 patients referred to LB (81; -37%) but with an increased NNS (6252) and overall cost (+$0.2M; +1%). **Conclusion:** In clinical trials screening for non-cirrhotic at-risk NASH, ruling-out F4 with FIB-4 followed by ruling-in at-risk NASH patients with NIS2+™ has the potential to significantly improve the recruitment process by reducing the LBFR, the number of F4 patients referred to LB and screening cost with a manageable NNS.

Table. Liver biopsy failures and number of cirrhotic patients referred to LB with RESOLVE-IT trial screening pathway vs FIB-4/NIS2+™ sequential pathway

	Resolve-IT Screening Pathway (RSP)	FIB-4 followed by NIS2+™ screening pathway			
FIB-4 cutoff	-	<2.67	<2.48	<2.67	<2.48
NIS2+™ cutoff	-	≥0.53	≥0.53	≥0.68	≥0.68
Performance metrics					
Sensitivity	-	0.78	0.77	0.60	0.59
Specificity	-	0.69	0.69	0.83	0.84
LR+	-	2.5	2.5	3.6	3.7
LR-	-	0.3	0.3	0.5	0.5
Performance to achieve 1000 inclusions					
NNS	3220	4630	4792	6023	6252
LBs performed, n	2522	1648	1646	1450	1442
LBFR (n)	60% (1522)	39% (648)	39% (646)	31% (450)	31% (442)
Positive liver biopsies	1000	1000	1000	1000	1000
Failures avoided vs RSP, n (% reduction)	NA	874 (-57%)	876 (-58%)	1072 (-70%)	1080 (-71%)
Number of cirrhotic patients referred for LB	128	98 (-23%)	89 (-30%)	93 (-27%)	81 (-37%)
Total cost of screening ($US M)	15.0	13.6 (-9%)	13.9 (-7%)	14.9 (-1%)	15.2 (+1%)

LR+, Positive Likelihood Ratio; LR-, Negative Likelihood Ratio

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♦ 2101-A | SERIAL VIBRATION CONTROLLED TRANSIENT ELASTOGRAPHY (VCTE)-BASED AGILE SCORES PREDICT LIVER-RELATED EVENTS IN NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) – A MULTICENTER COHORT STUDY OF 16,603 PATIENTS

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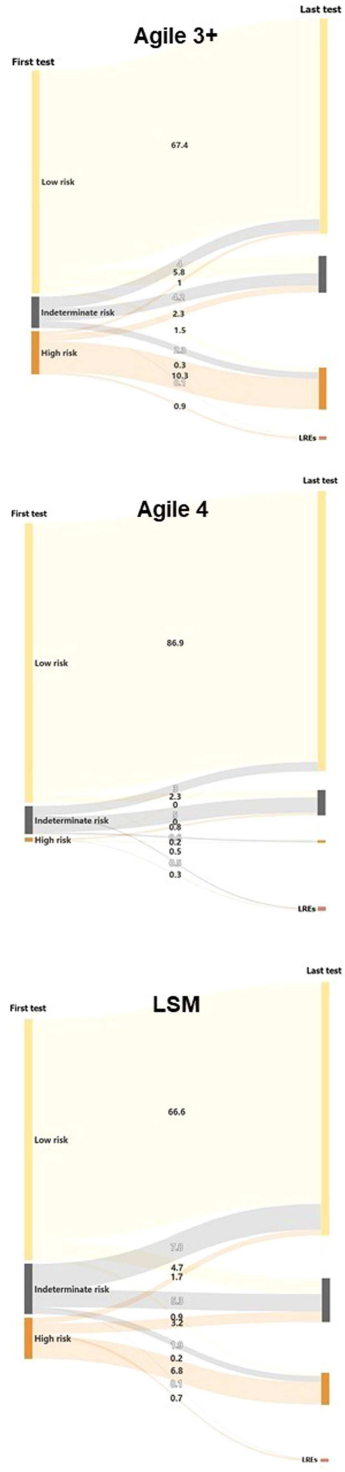
Background: The Agile scores – based on liver stiffness measurement (LSM) by VCTE, platelets, transaminases, diabetes, sex and age – were developed to refine the diagnosis of advanced liver fibrosis in NAFLD. Dynamic change of the scores over time and the corresponding clinical significance are currently unclear. We aimed to determine the prognostic implications of one-off and repeated Agile score assessments. **Methods:** This retrospective cohort study included data of patients with NAFLD who underwent VCTE examination at 16 centers in the Americas, Europe and Asia. The Agile scores were compared with LSM alone, FAST score and 6 other simple fibrosis scores. The primary outcome was liver-related events (LREs), defined as hepatocellular carcinoma or hepatic decompensation (ascites, variceal hemorrhage, hepatic encephalopathy or hepatorenal syndrome). **Results:** 16,603 patients with VCTE examination were included (age 55 ± 14, 57.8% male, median LSM 6.0 [IQR 4.7-8.5] kPa). At a median follow-up of 51.7 months, 316 (1.9%) patients developed LREs. Both Agile 3+ and Agile 4 scores classified fewer patients in the gray zone than LSM and most fibrosis scores and achieved the highest discriminatory power in predicting LREs (area under receiver-operating characteristic curve 0.87-0.90 at 3 and 5 years, compared with 0.78 for FAST and 0.86 for LSM). Among patients with Agile 3+ score < 0.451, 0.451-0.678, and ≥ 0.679, the incidence of LRE was 0.7, 3.3, and 24.9 per 1,000 person-years, respectively ($P < 0.001$). 10,921 patients had repeated VCTE at a median interval of 15 months and were included in the serial analysis. 81.9% and 92.1% of patients had stable Agile 3+ and Agile 4 scores (same risk categories at both assessments) (Figure). The incidence of LRE was 0.6 and 30.1 per 1,000 person-years in patients with persistently low and high Agile 3+ scores, respectively, while patients with changing risk categories between two visits had moderate risk. A similar trend was observed for the Agile 4 score, though it missed more LREs in the low-risk group. **Conclusion:** The Agile scores classify fewer patients into the gray zone than other noninvasive tests and have high stability on repeated testing. This translates into superior performance in predicting LREs.



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2102-A | SERUM CK18f IS AN INDICATOR OF LIVER INFLAMMATION, BALLOONING, AND PREDICTS INDICATION AND RESPONSE TO TREATMENT IN PATIENTS WITH NONALCOHOLIC STEATOTIC LIVER DISEASE

Miwa Kawanaka[1], Hirokazu Takahashi[2,3], Michihiro Iwaki[4], Ken Nishinio[5], Wenli Zhao[2], Masato Yoneda[4], Kenichi Tanaka[2], Hideki Fujii[6], Yoshihiro Kamada[7], Yoshio Sumida[8], Hirofumi Kawamoto[5], Atsushi Nakajima[4] and JSG-NAFLD, (1)Kawasaki Medical Center, Kawasaki Medical School, Okayama, Japan, (2) Saga University, (3)Division of Metabolism and Endocrinology, Faculty of Medicine, (4)Yokohama City University Graduate School of Medicine, (5)Kawasaki Medical Center, Kawasaki Medical School, (6)Osaka Metropolitan University, (7)Osaka University Graduate School of Medicine, (8)Aichi Medical University

Background: Although various noninvasive diagnostic methods to predict liver fibrosis in nonalcoholic steatotic liver disease (NASLD) have been developed, no such markers have available to predict inflammation, ballooning, and other nonalcoholic steatohepatitis (NASH) changes. Furthermore, there are few reports comparing changes in histology and changes in CK18f after repeated liver biopsies. The aim of this study was to investigate whether the apoptosis marker, serum cytokeratin 18 fragment (CK18f), can help predict the response to treatment in NASLD. In addition, serum CK18f and liver fibrosis markers were evaluated as biomarkers for predicting the NAFLD activity score (NAS) ≥ 4 and stage ≥ 2, crucial criteria for NASH clinical trials by the Food and Drug Administration (FDA). **Methods:** A total of 565 patients with NASLD (mean age 58 (18–85) years, male/female: 269/296; stages: 0/1/2/3/4 :49/141/142/198/35) and undergoing liver biopsy were enrolled. We investigated the relationship between serum CK18f and liver histology, ALT, AST, Γ-GTP, FIB-4 Index, and type IV collagen 7S. The liver fibrosis markers and CK18f were used to diagnose

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(Table 1). NOS at a revised cut-off (NOS < -2.3) identify more "low-risk" NAFLD patients than sequential testing of FIB-4/LSM (82.3% vs 76.6%) without missing more LRE (18.2% vs 18.2%). Both FIB-4, LSM and NOS has suboptimal performance to predict MACE in this cohort. **Conclusion:** The revised NOS cut-off (NOS < -2.3) may provide an alternative for population-based NAFLD risk-stratification, independent of VCTE. Validated tools in addition to fibrosis markers are needed to stratify MACE risk in NAFLD patients.

Table 1: Diagnostic performance of NOS, FIB-4 and LSM to predict the occurrence of liver-related events in NAFLD patients

Non-invasive tests (NITs)	Cut-off of NITs	Low-risk NAFLD	Missed LRE	Missed MACE
FIB-4 alone	FIB4 <1.3	440/747 (58.9%)	0/11 (0%)	9/18 (50%)
Sequential FIB-4 and NOS	FIB-4 < 1.3, then NOS < -1.3	771/747 (95.2%)	8/11 (72.7%)	15/18 (83.3%)
Sequential FIB-4 and LSM	FIB-4 < 1.3, then LSM < 8 kPa	572/747 (76.6%)	2/11 (18.2%)	11/18 (61.1%)
NOS	NOS <-1.3	708/747 (94.8%)	8/11 (72.7%)	14/18 (77.8%)
NOS	NOS <-2.3	615/747 (82.3%)	2/11 (18.2%)	10/18 (55.6%)

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2129-A | VALIDATION OF THE HISTOINDEX AI DIGITAL PATHOLOGY PLATFORM AS AN AIDING TOOL TO INCREASE PATHOLOGIST CONCORDANCE ON FIBROSIS STAGING IN NASH

Desiree Abdurrachim[1], Serene Lek[2], Yongqi Zhou[1], Chun Kit Wong[1], Charlene Zhi Lin Ong[1], Ashmita Saigal[3], Radha Krishnan[4], Geoffrey Walford[5], Elaine Lay Khim Chng[6], Dean Tai[6], Gideon Ho[6], Annaswamy Raji[7], Thomas Forest[8], Richard Baumgartner[9], Saswata Talukdar[3], Chih-Liang Chin[3], Samuel S. Engel[7], Asad Abu Bakar Ali[1], David E Kleiner[10] and Arun Sanyal[11], (1)Cardiometabolic Diseases, MSD, Singapore, (2) Clinnovate Health UK Ltd, UK, (3)Cardiometabolic Diseases, Merck & Co., Inc., South San Francisco, CA, (4)Global Clinical Development, MSD (UK) Limited, London, UK, (5)Translational Medicine, Merck & Co., Inc., Boston, MA, USA, (6)Histoindex Pte Ltd, Singapore, (7)Global Clinical Development, Merck & Co., Inc., Rahway, NJ, USA, (8)Non-Drug Safety, Merck & Co., Inc., West Point, PA, USA, (9)Biostatistics and Research Decision Sciences, Merck & Co., Inc., Rahway, NJ, USA, (10)Laboratory of Pathology, National Cancer Institute, Bethesda, MD, (11) Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA

Background: Intra- and inter-observer variability in histological staging of fibrosis in NASH clinical trials lead to suboptimal selection of patients and confound assessment of fibrosis response. Aim: To prospectively evaluate the utility of the HistoIndex artificial intelligence (AI) digital pathology tool to improve the reliability of fibrosis staging in NASH. **Methods:** Histology slides from two trials (NCT #03517540, #03912532) including 80 baseline/screening biopsies and 40 paired baseline and end-of-treatment biopsies were used. Four expert hepato-pathologists, masked to each other, read a total of 120 biopsy sections twice each, masked to study source, with and without the AI aiding tool respectively, in random order reading 30 biopsies each week. Following a washout period of 4 weeks, the process was repeated again. The AI aiding tool consisted of unstained second harmonic generation/two photon excitation fluorescence (SHG/TPEF) images and the AI quantitative fibrosis (qF) values. Pathologist median scores were considered the reference standard. Inter-observer kappa was computed. The impact of harmonization on need for adjudication using the current FDA-recommended approach to histological assessment was also determined. Significance was set at $P < 0.05$. **Results:** The fibrosis stage distribution (based on pathologist median without AI) is F0: 6, F1: 12, F2: 48, F3: 27, F4: 25. Compared to conventional reads, AI-assisted reads improved inter-observer kappa, with the greatest impact shown for F0-F2 population (figure). In clinical trials, this kappa improvement would have reduced the number of cases requiring adjudication by a third reader by 30%. The rates of concordance between 4 pathologists for inclusion of NASH with F2-F3 increased from 45% to 74% with AI; concordance on exclusion of other stage combinations increased from 38% to 55%. This was associated with decreased variance around the median reads. For masked assessment of treatment response, AI increased concordant assessment of fibrosis response from 49% to 61%. Overall, at least 3 out of 4 pathologists considered SHG/TPEF image useful in 83% cases and qF values useful in 55% cases; this was greatest for F1-F2. **Conclusion:** SHG/TPEF-based HistoIndex

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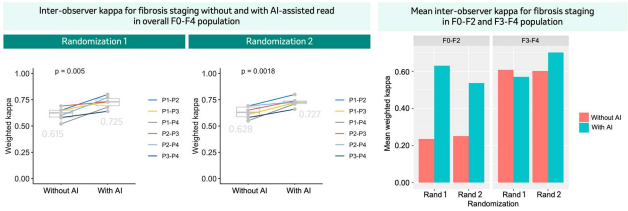
AI tool enhances pathologist confidence and inter-rater reliability for assessment of fibrosis stage in NASH. They validate the utility of SHG/AI as an aid for pathologist assessment of fibrosis. These data support the use of SHG/AI to enhance the efficiency of clinical trials and reliability of fibrosis readouts of response from trials.



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2130-A | WHAT PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE SHOULD WE TREAT WITH PHARMACOLOGICAL AGENTS?

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2137-A | AMONG PEOPLE WITH HIV, NON-HISPANIC BLACKS HAVE A SIGNIFICANTLY LOWER PREVALENCE OF NAFLD AND CLINICALLY SIGNIFICANT FIBROSIS

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Background: Racioethnic differences in the prevalence of NAFLD and clinically significant fibrosis (CSF) have been previously reported but this has been adequately investigated in people with HIV (PWH). We estimated racioethnic differences in the prevalence of NAFLD and CSF among PWH. **Methods:** This cross-sectional

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analysis includes PWH ≥20 years prospectively enrolled in two US multicenter studies from March 2018 to April 2023 who underwent VCTE examinations (Fibroscan®). NAFLD was defined by CAP ≥263 dB/m in the absence of excessive alcohol intake, steatogenic medications, and other causes of liver disease. CSF was defined as LSM ≥8 kPa. Self-reported racioethnic groups included non-Hispanic White (NHW), non-Hispanic Black (NHB), and Hispanic. Associations between racioethnic groups and the risk of NAFLD and CSF were examined via multivariable logistic regression models. **Results:** The study sample included 873 adults (mean age, 52 y; 72% men; 253 [29%] NHW, 409 [47%] NHB, and 211 [24%] Hispanic. NAFLD and CSF were present in 465 (53%) and 131 (15%) individual's, respectively. The prevalence of NAFLD was 60% for NHW, 43% for NHB, and 64% for Hispanics (overall $P < 0.01$). The prevalence of CSF was 22% for NHW, 11% for NHB, and 13% for Hispanic (overall $P < 0.01$). As compared with NHW, upon controlling for relevant co-variates (Table), NHB had lower risk of both NAFLD (Adj. OR: 0.37, 95% CI: 0.23-0.58) and CFS (Adj. OR: 0.44, 95% CI: 0.26-0.75). There was no difference in the risk of NAFLD and CSF between NHW and Hispanic ethnicity in the controlled analysis (Table). There was no association with antiretroviral therapy, CD4 cell counts, or HIV viral load (data not shown). In addition to race, age, body mass index (BMI), waist circumference, type 2 diabetes (T2D), ALT, and triglyceride levels were independently associated with the risk of NAFLD (Table). Age, BMI, waist circumference, T2D, hypertension, ALT, AST, and platelet count were independently associated with the risk of CSF (Table). **Conclusion:** Non-Hispanic Black race is associated with lower prevalence of NAFLD and clinically significant fibrosis, in comparison to NHW and Hispanic ethnicity in a large cohort of PWH. Hispanic ethnicity is not associated with a higher prevalence of CSF than NHW in this cohort. HIV related factors did not influence NAFLD prevalence. Social drivers of health and genetic factors may underlie these differences and require further study.

Results based on logistic multivariable analysis.

	NAFLD (CAP≥263 dB/m)		CSF (LSM≥8 kPa)	
Variable	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.03 (1.009-1.05)	<0.01	1.03 (1.006-1.05)	0.01
Race/ethnicity				
NH White	*Ref.* (1)	-	*Ref.* (1)	-
NH Black	0.37 (0.23-0.58)	<0.01	0.44 (0.26-0.75)	<0.01
Hispanic	1.10 (0.68-1.78)	0.69	0.72 (0.41-1.27)	0.26
BMI (kg/m²) [a]	1.25 (1.20-1.30)	<0.01	1.08 (1.05-1.12)	<0.01
Waist circumference (cm) [a]	1.09 (1.08-1.11)	<0.01	1.04 (1.02-1.05)	<0.01
T2D (yes)	2.11 (1.33-3.36)	<0.01	1.63 (1.00-2.68)	0.04
Hypertension (yes)	0.86 (0.59-1.24)	0.43	2.06 (1.23-3.45)	<0.01
ALT (U/L) [b]	1.01 (1.003-1.02)	<0.01	1.01 (1.005-1.02)	<0.01
AST (U/l) [b]	1.006 (0.99-1.02)	0.28	1.02 (1.009-1.03)	<0.01
Triglycerides (mg/dl)	1.005 (1.002-1.008)	<0.01	1.00 (0.99-1.00)	0.46
Platelet count	1.00 (0.99-1.00)	0.28	0.99 (0.99-0.99)	0.01

[a] BMI and waist circumference were included in different models to avoid collinearity issues (r=0.86).
[b] ALT and AST were included in different models to avoid collinearity issues (r=0.71).

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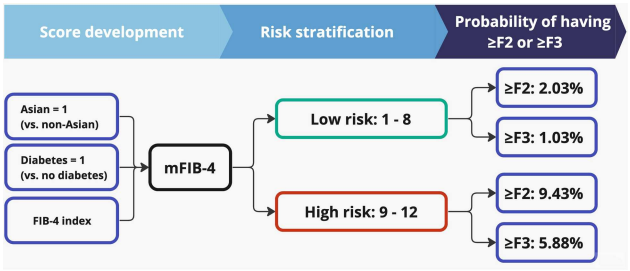

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2159-A | DIABETICS ON INSULIN THERAPY HAVE SIGNIFICANTLY HIGHER ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) BURDEN AND PROBNP CAN DISCRIMINATE ASCVD WITH HIGH SPECIFICITY IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Puneet Puri[1,2], Gowthami Kanagalingam[1,2], Bryan Badal[1,2], Joyce Xiyuan Badal[3], Benjamin Blake[4], Joelle Lemmons[1], Zenaida Malpaya[1], April Morris[1], Maribeth Capuno[1], Ashley Long[1], HoChong Gilles[1], Joseph Spataro[1,2], Jennifer Miller[1,2], Jasmohan S. Bajaj[1,2], Brian C. Davis[1,2], M. Rehan Khan[1], Ion Jovin[1] and Michael Fuchs[1,2], (1)Mcguire Richmond VA Medical Center, (2)Virginia Commonwealth University, (3) University of Toledo College, (4)Weill Cornell Medical College

Background: Cardiovascular (CV) morbidity and mortality is high in patients with nonalcoholic fatty liver disease (NAFLD). Diabetics are at high risk of CV disease (CVD). We aimed to examine this CVD burden and impact of insulin vs. non-insulin therapies in patients with NAFLD which is not well described. **Methods:** NAFLD patients were prospectively evaluated for presence of cardiovascular disease (CVD). The diagnosis of NAFLD was established either on imaging (Vibration Controlled Transient Elastography [VCTE] and MRI Proton Density Fat Fraction [PDFF]) or liver histology. A 10-year FRS was calculated and those with intermediate ($>10\%$) and high ($>20\%$) risk were offered CT heart to assess for coronary artery calcium (CAC) score. A CAC score of 0 is considered optimal, while CAC score of 1-99 is low risk, 100-399 is intermediate risk and 400 or greater is high risk atherosclerotic burden. Fasting blood samples for traditional CVD risks were also performed. Statistical analysis were performed using JMP. **Results:** Total of 201 Veterans (84% male) with mean ($\pm$SD) age of 56.6 $\pm$ 10 years were studie. Histologic evaluation was available on 128 with 17.5% at-risk NASH (F2 fibrosis or higher). 21/201 (10.5%) had pre-existing coronary artery disease (CAD) at time of presentation. Almost 100% of those were on aspirin and statin therapy. 27 (13.4%) had no diabetes, 59 (29.3%) had prediabetes, 115 (57.2%) had diabetes. Statin use was seen in 135 (67.5%) and 98 (48.8%) were taking aspirin and 81 (40.3%) were on both aspirin and statin. A CAC score ≥ 1 indicated CAD and was seen in 60% (73/121 coronary CT scans). Diabetics compared to non-diabetics had ~3 fold higher median Framingham heart risk (FHR) score (13, IQR 8-25) vs. (35, IQR 19-49; $p<0.0001$). Notably, no significant differences were noted between diabetics, non-diabetics and prediabetics for CAC scores. Among diabetic patients insulin also had a higher Framingham risk score compared to non-insulin therapy (28, IQR 18-45) vs. (45, IQR 35-56), $p=0.001$. CAC score (231, IQR 12-1572 vs 6.5, IQR 0-403, $p=0.009$). Based on CAC score those on insulin therapy had higher risk of coronary artery disease (OR 4.5; 1.2-17.3). FHR score was two folds higher in those with either statin or aspirin use (33, IQR 19-46 vs. 17.2, IQR 11-27 $p<0.0001$. However, Framingham risk score was 2.5 fold higher in statin and ASA users compared to non-users (35% vs 14%, $p<0.0001$). Those that had evidence of coronary artery disease based on CAC score 23% were not on statins. Amongst those who had severe CAD (CAC score >100) about 20% were not on statins. Pro-BNP had an area under the curve of 0.77 with CI 0.64-0.87, $p<0.0001$ with YODEN index of 0.48. Specificity 92% for cutoff >49). **Conclusion:** NAFLD patients with diabetes on insulin have high risk of CAD and pro-BNP can discriminate CAD with high specificity

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2160-A | DIAGNOSIS IS DELAYED: PERICOMPLICATION DIAGNOSIS OF NONALCOHOLIC FATTY LIVER DISEASE

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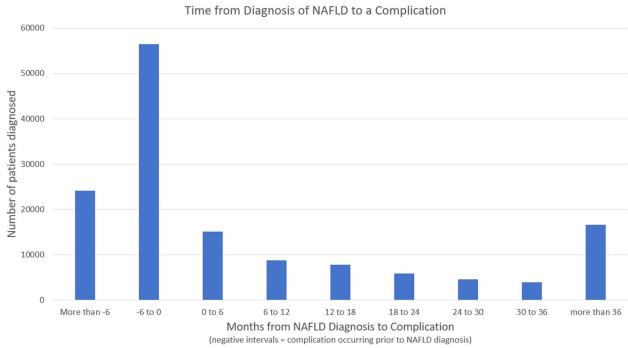
Background: Nonalcoholic fatty liver disease (NAFLD) is a condition in which screening guidelines remain controversial as the characteristics that predispose to the development of complications remain unclear. An earlier diagnosis of NAFLD may allow adequate time for intervention and help prevent complications such as hepatocellular carcinoma (HCC), cirrhosis, or advanced liver disease requiring a liver transplant. Our aim was to determine the proportion of patients with a delayed diagnosis of NAFLD, defined as patients diagnosed with NAFLD within 6 months or after a complication like HCC, cirrhosis or liver transplant. **Methods:** This is a retrospective analysis of patients within the Truven MarketScan database (1/2007-12/2021), a claims database for more than 250 million U.S. people with private insurance. All adults ≥ 18 years who had a diagnosis of NAFLD, a liver complication (defined as HCC, cirrhosis or liver transplant), and had at least 12 months of insurance coverage prior to the first liver complication were included. **Results:** The study population included 143,310 patients with a diagnosis of NAFLD and at least one associated liver complication. The mean age was 56.3 ± 14.0 years and 53% were female. Two-thirds of the patients (95,843, 66.8%, $p < 0.001$) were diagnosed with NAFLD less than six months before or even after the development of a liver complication (Figure). Patients with a pericomplication diagnosis of NAFLD were more likely to be older (57.6 ± 14.5 vs. 53.8 ± 12.5), have cardiovascular disease (13.7% vs. 5.5%), hypertension (72.2% vs. 68.4%), diabetes (45.7% vs. 43.2%), chronic kidney disease (16.7% vs. 7.1%), obesity (36.2% vs. 31.1%), tobacco use (18.7% vs. 12.6%) and illicit drug use (2.3% vs. 1.4%), all $P < 0.001$. The mean Charlson Comorbidity Index (CCI) was significantly greater in this group compared to patients that were diagnosed earlier (mean 3.0 ± 3.0 vs 1.9 ± 2.3, $p < 0.0001$). On multivariable logistic regression adjusted for age, sex, and CCI, a first visit with a medical provider specializing in gastroenterology (OR 0.32, 95% CI 0.31-0.32, $p < 0.001$), cardiology, endocrinology, or nephrology (OR 0.44, 95% CI 0.43-0.45, $p < 0.001$) more than 1 year prior to a complication was associated with a significantly lower odds of delayed diagnosis of NAFLD. **Conclusion:** Diagnosis of NAFLD in real-world patients is severely delayed, with 2 in 3 patients diagnosed either after or within 6 months from a liver complication. Patients followed longitudinally by medical providers in gastroenterology and other metabolic specialties for one year or greater had a lower risk of an early complication. Early diagnosis and continued follow-up of NAFLD does delay the risk of developing the devastating complications of this condition.



Disclosures: The following people have nothing to disclose: Richie Manikat, Leslie Yeeman Kam

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Therefore, we aimed to map the evolution of NAFLD and the influence of statin treatment in a primary care (PC) cohort assessed by liver stiffness (LSM) and controlled attenuation parameter (CAP™). **Methods:** In a prospective, multicentric cohort study in two large PC practices in Belgium between October 2020 and May 2023, a FibroScan® measurement (for assessment of steatosis by CAP™ and of LSM as a surrogate for fibrosis) and clinical examination (waist circumference (WC) and BMI) was performed at baseline and follow-up. Steatosis was defined as a CAP™ value > 215 dB/m. At the start, lifestyle advice was given. Recent laboratory data, medical background, and medication for both study visits were gathered from the electronic patient file. **Results:** Of the 67 study participants evaluated, 11 (16.4%) were excluded due to treatment with tamoxifen, not being sober, alcohol abuse, or IQR/MED > 30%. In total, 56 (83.6%) participants were included, of whom 21 (37.5%) were men, 55 (94.0%) were of Caucasian origin, and 40 (71.7%) had steatosis. The mean age, median BMI, and mean WC at baseline were 62 ± 10 years, 26.3 ± 6.0 kg/m², and 91.3 ± 12.2 cm, respectively. At follow-up, WC (91.7 ± 12.5 vs. 95.9 ± 11.2 cm; $p < 0.001$) and CAP™ (251.4 ± 62.8 vs. 261.2 ± 56.0 dB/m; $p = 0.005$) were significantly higher while BMI remained unchanged ($p = 0.098$). LSM and the serum level of triglycerides decreased significantly (5.2 ± 2.3 vs. 4.3 ± 1.5 kPa; $p = 0.021$ and 102 ± 62 vs. 87 ± 37 mg/dl; $p = 0.008$). No statistical differences were found for the liver enzymes AST, ALT, and GGT. Twenty of the 56 (64.3%) participants took statins and 2 (3.6%) fibrates. No statistical difference between baseline and follow-up was seen for CAP™ for statin users (246.5 ± 64.1 vs. 265.4 ± 58.1 dB/m; $p = 0.266$) and non-users (254.3 ± 62.9 vs. 258.7 ± 55.9 dB/m; $p = 0.691$). Non-statin users saw a significant decrease in LSM (5.5 ± 2.6 vs. 4.4 ± 1.3 kPa; $p < 0.001$) at follow-up, which was not seen with statin users (5.3 ± 2.0 vs. 4.3 ± 2.2 kPa; $p = 0.179$). **Conclusion:** Overall, we saw a decrease in fibrosis and triglycerides during the two-year follow-up time in a Caucasian PC cohort. No study participant developed decompensated liver disease. However, we did see an increase in steatosis accompanied by an increase in waist circumference, although lifestyle advice was given during the first visit. Moreover, statin use did not influence steatosis or fibrosis evolution, though future research is warranted to further investigate the influence of statin treatment on NAFLD.
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2180-A | FOOD INSECURITY IS ASSOCIATED WITH LOWER NAFLD PREVALENCE BUT GREATER LIVER FIBROSIS IN PEOPLE WITH HIV

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Background: Food insecurity, defined as the economic or social condition of limited or uncertain access to nutritionally adequate foods, is a growing public health problem in the US. In recent years, it has emerged as a risk factor for nonalcoholic fatty liver disease (NAFLD) and advanced liver fibrosis in the general population. However, little is known about the impact of food insecurity on liver disease in people with HIV (PWH). We aimed to examine associations between food insecurity and NAFLD and liver fibrosis prevalence in a diverse multicenter cohort of PWH. **Methods:** PWH aged 20 years on suppressive antiretroviral therapy, HIV RNA < 200 copies/mL, and without chronic viral hepatitis or other known cause of liver disease were screened for NAFLD and fibrosis by vibration controlled transient elastography at 8 US centers. NAFLD was defined as CAP ≥ 263 decibels/m in the absence of self-reported heavy alcohol use and advanced fibrosis was defined as liver stiffness measurement (LSM) ≥ 10 kPa. Food security was measured using the validated Six-Item Short Form US Household Food Security Survey Module, and participants were categorized as being food secure or food insecure. We used multivariable logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) of NAFLD and advanced fibrosis by food security status. **Results:** Among 570 PWH, mean age was 54 years, 410 (72%) were male, 26% White, 49% Black, 21% Hispanic, 267 (47%) had BMI ≥ 30 kg/m², and 171 (30%) were diabetic. NAFLD was present in 306 (54%) and advanced fibrosis in 45 (8%) of participants. Food

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insecurity was present in 175 (31%) of the entire cohort, 84 (27%) of those with NAFLD, and 21 (47%) of those with advanced fibrosis. Among the entire cohort, participants who were food insecure were less likely to have type 2 diabetes (25% vs 32%) and undetectable HIV-1 RNA (76% vs 85%) compared to those who were food secure ($P < 0.05$ for all) but there were no differences in age, body mass index (BMI), or race and ethnicity. In a fully covariate-adjusted analysis, food insecurity was associated with a lower risk of NAFLD (OR = 0.51 [95% CI: 0.31-0.83], $P < 0.01$) (Table). By contrast, food insecurity was associated with a higher risk of advanced fibrosis among the entire cohort (OR = 2.32 [95% CI: 1.15-4.67], $P = 0.02$) after adjustment for age, sex, race and ethnicity, BMI, physical activity, and education level (Table). **Conclusion:** Food insecurity is highly prevalent among adult PWH and is associated with a lower risk of NAFLD but a greater risk of advanced fibrosis. Our findings suggest that food insecurity in PWH may contribute to hepatic fibrosis through mechanisms other than hepatic steatosis. Further studies are needed to confirm our observations and to better understand their mechanisms and implications.

Table. Multivariable logistic regression* of food security and the risk of NAFLD (CAP ≥263 decibels/m) and advanced fibrosis (LSM ≥10 kPa) in the entire cohort (N=570)

	NAFLD		Advanced fibrosis	
	OR (95% CI)	P value	OR (95% CI)	P value
Food insecure (reference: food secure)	**0.51 (0.31-0.83)**	**<0.01**	**2.32 (1.15-4.67)**	**0.02**
Male sex	1.52 (0.88-2.65)	0.13	2.42 (0.97-6.02)	0.06
Race				
Non-hispanic White	Ref. (1)	-	Ref. (1)	-
Non-hispanic Black	0.41 (0.23-0.72)	<0.01	0.26 (0.11-0.62)	<0.01
Hispanic	1.57 (0.81-3.05)	0.18	0.41 (0.14-1.19)	0.10
Body mass index (per unit increase)	1.25 (1.19-1.31)	<0.01	1.13 (1.07-1.19)	<0.01
Type 2 diabetes (reference: no diabetes)	2.57 (1.56-4.23)	<0.01	2.89 (1.40-5.96)	<0.01
Physical activity (met/min/week)	0.99 (0.99-1.00)	0.49	0.99 (0.99-1.00)	0.54

*Multivariable models adjusted for covariates listed in the table as well as age and education level.

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Disclosure information not available at the time of publication: Audrey Lloyd, Susanna Naggie, Mark S Sulkowski, Jordan E. Lake, Holly Crandall, Laura Wilson, Sonya Heath

2181-A | GASTROINTESTINAL MALIGNANCIES IN HOSPITALIZED PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD): ANALYSIS OF THE NATIONAL INPATIENT SAMPLE (NIS)

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Background: It is estimated 1.5 billion people worldwide have some element of chronic liver disease (CLD) or cirrhosis.[1] Non-alcoholic fatty liver disease (NAFLD) has become the most common cause of CLD, affecting up to 30% of the world population.[1,2] It is well known cirrhosis is the strongest risk factor for the development of hepatocellular carcinoma. However, several studies have shown the association of NAFLD and the development of extra hepatic malignancies, specifically an increased risk of gastrointestinal malignancies.[2-5] The aim of this study was to determine the incidence of gastrointestinal malignancies (esophagus, gastric, colorectal, pancreatic) for patients with NAFLD compared to controls without NAFLD using an adult inpatient population. **Methods:** Using a population based retrospective study design, we analysed data from the United States Nationwide Inpatient Sample (NIS) database for 2013. Using validated International Classification of Diseases, Ninth Revision (ICD-9) codes we identified inpatients 18 years or older with NAFLD and a diagnosis of a gastrointestinal malignancy (esophagus, gastric, colorectal, pancreatic). We then compared that cohort to adult inpatients without NAFLD. We adjusted for multiple confounders (age, payer type, location, hypertension, dyslipidemia, obesity, type 2 diabetes mellitus, chronic kidney disease, smoking, alcohol and cirrhosis) and performed a multivariable logistic regression analysis to evaluate the impact of NAFLD on gastrointestinal related malignancies. **Results:** Utilizing the NIS database we were able to identify 36,597,790 potential patients to include in the study. 235,035

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2201-A | INCREASING INCIDENCE AND PREVALENCE OF HCC AND CIRRHOSIS IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

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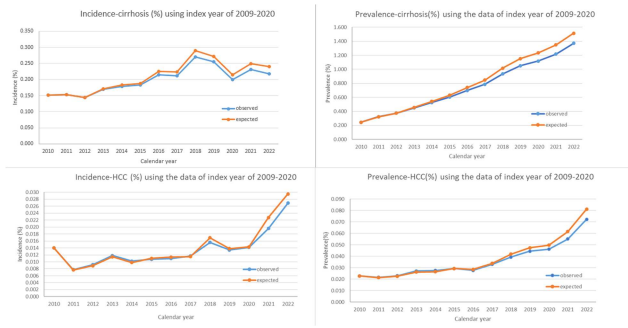
Background: Patients with nonalcoholic fatty liver disease (NAFLD) are at risk for developing costly and morbid complications, although the actual incidence and prevalence of these complications is unknown. We examined time trends in the incidence and prevalence of cirrhosis and hepatocellular carcinoma (HCC). **Methods:** We calculated the annual incidence and prevalence of cirrhosis and HCC in a national sample of Veterans identified as having NAFLD based on a previously validated algorithm between 2010 and , with follow up until 12/31/2022. We used ICD-9/10 codes to define cirrhosis and used a combination of Veterans Affairs (VA) Cancer Registry and manual review of patient charts to confirm HCC cases. We used direct standardization using the age distribution of 2010 as the standard to adjust the incidence and prevalence rates for aging of the cohort. We compared the incidence and prevalence in the first year *versus* the last year using a chi-square test. **Results:** In this cohort, the number of individual's with NAFLD increased from 17,413 in 2011 to 49,796 in 2022. The mean age of the yearly cohorts increased from 54.1 years in 2011 to 58.6 years in 2022. There was no significant change in gender distribution. The annual age-standardized incidence rates of cirrhosis increased over time from 1.5 per 1000 persons in 2011 to 2.4 per 1000 in 2022 (p-value < 0.0001). HCC age-standardized incidence rose from 0.08 per 1000 in 2011 to 0.3 per 1000 persons with NAFLD in 2022 ($p < 0.0001$. The prevalence of cirrhosis increased 5-fold from 3 per 1000 in 2011 to 15 per 1000 persons in 2022 ($p < 0.0001$). The prevalence of HCC rose by 3-fold from 0.2 to 0.8 per 1000 persons in 2022 ($p < 0.0001$). **Conclusion:** In a U.S. population with NAFLD, the annual incidence of HCC is low but rising over time. This increase is not explained by the ageing of the study cohort but could be related to progression of liver fibrosis over time. Both the incidence and prevalence of cirrhosis in patients with NAFLD increased over the last decade. Given the absence of targeted screening and effective treatments for NAFLD, the burden of NAFLD cirrhosis and HCC will continue to grow although it is unlikely to reach high proportions in the next decade.



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Disclosure information not available at the time of publication: Basim Ali, Jennifer Kramer, Yumei Cao, Ruben Hernaez, Hashem B. El-Serag

2202-A | INCREASING INCIDENCE OF NON-ALCOHOLIC FATTY LIVER DISEASE IN OLDER ADULTS: A POPULATION-BASED TIME-TREND ANALYSIS USING THE GLOBAL BURDEN OF DISEASES STUDY 2019, 1990-2019

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Background: Non-Alcoholic Fatty Liver Disease (NAFLD) incidence and prevalence rates have dramatically elevated; however, there are limited data about recent US age and gender-specific NAFLD incidence trends. The aim of this study is to conduct a time-trend analysis of age and gender-specific NAFLD incidence rates in the US using the Global Burden Diseases (GBD) 2019 database. **Methods:** Data was obtained from the GBD 2019 database, an International database that covers 100% of NAFLD diagnosed cases in the US. NAFLD incidence rates, age-adjusted to the standard US population, were calculated using SEER*Stat software (v.8.4.0.1, National Cancer Institute "NCI") and were stratified by gender, as reported in the database. Time-trends were estimated as annual percentage change (APC) and average APC (AAPC) using Joinpoint Regression

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Software (v.4.9.0.1, NCI) utilizing Monte Carlo permutation analysis to generate the simplest trend. Pairwise comparison was conducted between gender-specific trends using the tests of parallelism and coincidence. Age-specific trends were also assessed in two age sub-groups: younger adults aged 15-49 years and older adults aged 50-74 years. A two-sided P-value cut-off of 0.05 was utilized for statistical significance. **Results:** In 2019, there were 4.1 million patients diagnosed with NAFLD in the US. Overall, incidences rates have been increasing significantly in older adults but not younger adults (AAPC = 2.2 vs 0.8, AAPC difference = 1.4, $P < 0.001$). Age-specific trends were not identical ($P < 0.001$) nor parallel ($P < 0.001$) suggesting that NAFLD incidence rates are different and increasing at a greater rate compared to younger adults. Similarly, female's incidence rates have been increasing significantly higher than males (AAPC = 1.2 vs 1.0) with an AAPC difference between females and males of 0.2 (= 0.027), suggesting that the disparity between NAFLD incidence trends between age-specific groups arises from women. **Conclusion:** Our results suggest that NAFLD incidence trends have been increasing in older adults while stable in younger adults over the last three decades. The greatest difference between older and younger adults seemed to be arising from older women. While this increase can be due to high obesity rates and sedentary lifestyle, it can also represent a true increase in incidence. Future studies are warranted to investigate risk factors associated with the increasing incidence in older adults, especially in older women.

Trend analysis of Non-Alcoholic Fatty Liver Disease Age-Standardized Incidence rate with Gender and Age Variations from 1990 to 2019

Incidence	Trends[a]			Gender/Age-specific AAPC difference (95% CI)[b]	Pairwise comparison P-values		
	Time period	APC (95% CI)	AAPC (95% CI)		Gender/Age-specific AAPC difference	Coincidence[c]	Parallelism[d]
Gender							
Male	1990-1995	2..2 (2.0 to 2.4)	1.0 (0.8 to 1.1)	0.2	0.027	<0.001	<0.001
	1995-2000	-1.2 (-1.5 to -0.9)					
	2000-2007	0.2 (0.0 to 0.4)					
	2007-2014	1.0 (0.8 to 1.1)					
	2014-2017	4.5 (3.4 to 5.5)					
	2017-2019	0.6 (-0.4 to 1.6)					
Female	1990-1994	1.9 (1.6 to 2.1)	1.2 (1.0 to 1.3)				
	1994-2005	-0.3 (-0.4 to -0.2)					
	2005-2010	1.3 (1.0 to 1.6)					
	2010-2014	2.6 (2.2 to 3.1)					
	2014-2017	3.9 (3.0 to 4.8)					
	2017-2019	0.7 (-0.2 to 1.5)					
Age							
50-74 years	1990-1992	6.9 (5.3 to 8.5)	2.2 (2.0 to 2.4)	1.4	<0.001	<0.001	<0.001
	1992-1995	4.5 (3.0 to 6.1)					
	1995-2006	0.3 (0.2 to 0.4)					
	2006-2011	2.7 (2.2 to 3.2)					
	2011-2017	3.4 (3.0 to 3.7)					
	2017-2019	0.1 (-1.4 to 1.6)					
15-49 years	1990-1992	3.6 (2.8 to 4.3)	0.8 (0.7 to 1.0)				
	1992-1995	1.9 (1.2 to 2.7)					
	1995-2009	-0.5 (-0.5 to -0.4)					
	2009-2014	1.0 (0.8 to 1.3)					
	2014-2017	4.0 (3.2 to 4.7)					
	2017-2019	0.5 (-0.2 to 1.3)					

[a] Time-trends were computed using Joinpoint Regression Program (v4.9.0.1, NCI) with 5 maximum joinpoints allowed (5-line segments).
[b] Tests whether age/gender-specific trends were identical. A significant P-value indicates that the trends were not identical (i.e., they had different incidence rates and coincidence was rejected).
[c] Tests whether age/gender-specific trends were parallel. A significant P-value indicates that the trends were not parallel (i.e., parallelism was rejected).

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2203-A | INCRETIN-BASED THERAPIES, AND SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS AND RISK OF NEW-ONSET NONALCOHOLIC FATTY LIVER DISEASE AND HEPATOCELLULAR CARCINOMA AMONG PATIENTS WITH TYPE 2 DIABETES IN THE UNITED STATES: A NATIONWIDE REAL-WORLD LARGE POPULATION-BASED COHORT STUDY

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Background: Nonalcoholic fatty liver disease (NAFLD) is highly prevalent among patients with type 2 diabetes mellitus (T2DM). There has been a growing interest in the effects of second-line anti-diabetic drugs, such as glucagon-like peptide 1 receptor agonists (GLP-1 RA) and sodium–glucose cotransporter-2 inhibitors (SGLT-2i), on reducing hepatic fat content beyond their glucose-lowering effects. The association between these drugs and the risks of NAFLD and hepatocellular carcinoma (HCC) has not been explored in the US population. Thus, we aimed to determine whether GLP-1 RA and SGLT-2i are associated with a decreased risk of new onset of NAFLD and HCC compared with dipeptidyl peptidase-4 inhibitors (DPP-4i) among patients with T2DM. **Methods:** We conducted a population-based, retrospective cohort study with consecutive adult patients diagnosed with T2DM using TriNeTx dataset. Cohort entry was defined as the date of the first-ever prescription for one of the drugs of interest (GLP-1 RA or SGLT-2i, compared to DPP4i) during the study period. We used a lag of 6 months for all exposures to minimize protopathic bias. We performed a 1:1 propensity score matching (PSM) to reduce confounding effects. The primary outcomes were defined as the first incidence of NAFLD and HCC. We conducted a secondary and sensitivity analysis to assess the robustness of our findings. The outcomes were estimated using a Cox proportional hazards model

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2220-A | MEDICATIONS FOR WEIGHT LOSS AND NASH: A NATIONAL SURVEY OF PROVIDER ATTITUDES, PRACTICES AND KNOWLEDGE

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Background: Weight loss is the cornerstone of treatment in nonalcoholic fatty liver disease (NAFLD), including nonalcoholic steatohepatitis (NASH). While there are currently nine FDA-approved medications for weight loss, they are often underutilized in patients with NAFLD/NASH. Our aim was to perform a national survey of provider attitudes, practices and knowledge regarding weight loss and medication use in patients with NAFLD. **Methods:** We conducted a national U.S. survey of hepatology and gastroenterology providers from 2/6/23 to 3/13/23. Surveys were sent to 747 providers with 304 complete responses (41%) from 44 states and the District of Columbia. Respondents were a diverse group (50% women, 55% White) of mostly early career (46% < 5 y out of training) hepatologists (74%) working in an academic medical center with a liver transplant program (86%). **Results:** A significant majority of providers (78%) see ≥ 5 patients with NAFLD per week, of whom < 25% are taking medications for weight loss or NASH. While nearly all (96%) respondents believed weight loss medications could benefit patients with NAFLD, 77% have never/rarely prescribed them due to low comfort (81%). Amongst prescribers, the glucagon-like peptide-1 receptor agonists (GLP-1RA) were preferred (66%) compared to < 5% each for other FDA-approved weight loss medications. (Figure 1) In contrast, 63% have prescribed medications for NASH in the past 12 months, most commonly vitamin E, GLP-1RA, and statins, with positive correlation to NASH patient volume ($p < 0.05$). (Figure 2) The top perceived barriers to prescribing weight loss medications were lack of training/unfamiliarity, cost, and side-effects. Dedicated obesity clinics were more common than for NASH (79% v 28%, $p < 0.05$). Most providers (87%) reported low formal obesity education during their training and nearly all (95%) agreed for its inclusion in GI/hepatology fellowship training. Only one-third of FDA-approved weight loss medications were correctly identified by > 50% of providers regardless of experience, demonstrating a knowledge gap. In contrast, 73% accurately recognized that there are no FDA-approved medications for NASH. Advanced practice providers, trainees and those with < 5 years of experience were more likely to incorrectly identify vitamin E, pioglitazone and semaglutide as FDA-approved medications for NASH ($p < 0.05$). **Conclusion:** This nationwide survey demonstrates that while off-label prescribing for NASH was common, there were low rates of weight loss medication prescribing due to low comfort from insufficient education despite strong beliefs that they can benefit patients with NAFLD.

Figure 1. Prescribing patterns for weight loss medications

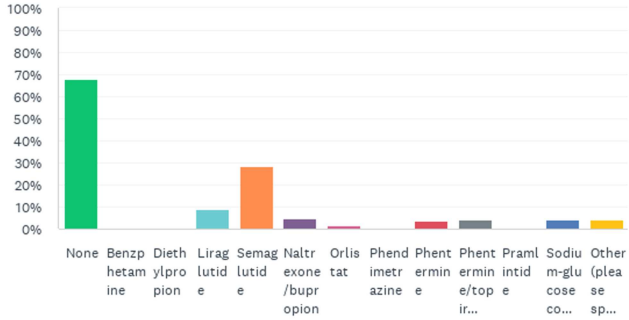
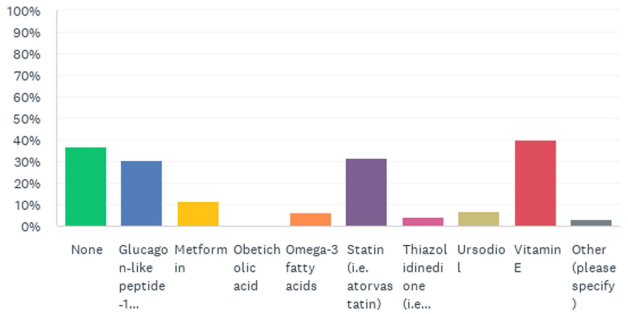


Figure 2. Prescribing patterns for NASH medications



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2221-A | METABOLIC CONTROL WORSENS WITH INCREASING FIBROSIS STAGE IN PATIENTS WITH PRE-CIRRHOTIC NONALCOHOLIC STEATOHEPATITIS (NASH): COMBINED DATA FROM MULTIPLE THERAPEUTIC CLINICAL TRIALS INCLUDING MORE THAN 6,000 PATIENTS (WITH THE COLLABORATION OF NAIL-NIT CONSORTIUM)

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Background: Metabolic comorbidities are well-established risk factors for nonalcoholic steatohepatitis (NASH) and liver fibrosis. Metabolic derangement has been hypothesized to independently contribute to the severity of NASH fibrosis stages. We aimed to describe patients' characteristics and liver histology across different group's metabolic comorbidities. **Methods:** We combined screening data from 7 non-cirrhotic therapeutic NASH trials. Patients were classified according to the 5-tier NASH CRN fibrosis stages (F0 to F4). Patients characteristics were described across fibrosis stages. **Results:** Out of the 6,558 patients, 2,271 with liver histology, clinical and laboratory data were included. The liver histology results and patients' characteristics in each group are shown in the Table. Across fibrosis stages, glycated hemoglobin (HbA1c) ($p < 0.001$) and fasting plasma glucose (FPG) ($p < 0.001$) increased from F1 to F3. Low density lipoprotein cholesterol (LDL) was lower in fibrosis stages F3-F4 compared to fibrosis stages F0 to F2. No trend was seen for other lipid parameters (high density lipoprotein HDL-cholesterol and triglycerides). In patients with cirrhosis, HbA1c and FPG were significantly lower. Uric Acid decreased consistently from F1 to F4. Waist and Hip circumferences increased from F1 to F3, but BMI was not significantly different between fibrosis stages. No effect was seen for CRP or Fibrinogen. Hispanic ethnicity tended to have earlier fibrosis stages compared to non-Hispanic populations. Similarly, males tended to have earlier fibrosis stages compared to females. **Conclusion:** Among the metabolic comorbidities, glycemic control worsens in patients with precirrhotic NASH with increasing fibrosis stages, while lipid panels and markers of inflammation are not different between fibrosis stages. Additional studies are needed to further confirm the independent association of HbA1c with NASH severity.

Fibrosis Stage	F0 N=389	F1 N=638	F2 N=515	F3 N=627	F4 N=102	p-value
	Mean (SD) or median or %					
NAS	2	4	5	5	4	
NASH						
No NASH	97.4%	56.3%	19.0%	9.7%	25.5%	
NASH	2.6%	43.7%	81.0%	90.3%	74.5%	
Gender						
Female	57.1%	53.0%	62.1%	61.4%	74.5%	<0.001
Male	42.9%	47.0%	37.9%	38.6%	25.5%	
Ethnicity						
Hispanic/Latino	50.1%	47.6%	43.0%	38.5%	42.2%	<0.001
Not Hispanic/Latino	49.9%	52.4%	57.0%	61.5%	57.8%	
Age						<0.001
18-25	4.6%	1.6%	1.4%	0.8%	0	
25-35	7.7%	6.7%	6.2%	3.5%	2.0%	
35-45	13.9%	16.1%	14.2%	10.8%	6.9%	
45-55	28.8%	29.3%	31.5%	29.8%	22.5%	
55-65	29.3%	31.5%	31.5%	34.1%	45.1%	
65-75	14.8%	13.9%	14.4%	19.8%	20.6%	
75-85	0.8%	0.8%	1.0%	1.1%	2.9%	
BMI	38.5 (7.9)	37.1 (7.6)	37.1 (6.8)	37.0 (6.6)	36.2 (5.2)	0.316
Waist Circumference	105 (33)	107 (31)	113 (24)	112 (22)	98 (33)	0.209
Hip Circumference	108 (33)	111 (33)	116 (25)	115 (23)	99 (33)	0.530
FPG	99.6 (26.8)	113.4 (39.0)	116.6 (34.0)	120.4 (34.5)	124.8 (38.5)	<0.001
HbA1c	6.0 (0.8)	6.4 (1.1)	6.5 (1.1)	6.7 (1.1)	6.6 (1.1)	<0.001
LDL	108 (40)	105 (38)	107 (38)	96 (37)	97 (31)	<0.001
HDL	46 (15)	44 (14)	44 (13)	45 (13)	47 (11)	0.840
Triglycerides	152 (76)	167 (92)	168 (86)	159 (81)	149 (67)	0.720
Uric acid	6.2 (1.3)	6.0 (1.4)	5.9 (1.4)	5.8 (1.4)	5.7 (1.4)	0.001
CRP	0.87 (1.3)	0.97 (1.8)	1.7 (4.2)	1.4 (3.6)	2.1 (6.3)	0.016
Fibrinogen	363 (74)	362 (78)	357 (86)	364 (83)	355 (83)	0.824

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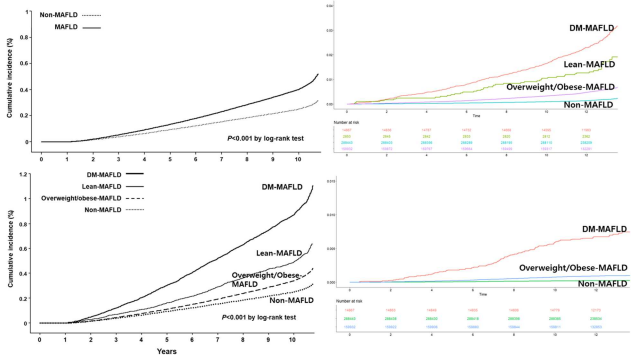
ity. We also examined cirrhosis and hepatocellular carcinoma risks in various MAFLD subgroups using the UK Biobank (UKB) dataset as a validation cohort. The UKB dataset included 466,162 individual's of Caucasian ethnicity. **Results:** Of the study subjects, 2,500,080 (33.5%) had MAFLD. During the median follow-up of 10.3 years, 20,843 patients (0.28%) developed liver-related complications. The MAFLD group had a higher overall risk of liver-related complications than the non-MAFLD group (adjusted cause-specific hazard ratio [aCHR] = 1.24; 95% confidence interval [CI] = 1.21–1.28; $P < 0.001$). The DM-MAFLD group showed a significantly higher risk of liver-related complications compared to the non-MAFLD group (aCHR = 1.82; 95% CI = 1.74–1.91; $P < 0.001$), followed by the lean-MAFLD group (aCHR = 1.22; 95% CI = 1.12–1.33; $P < 0.001$), and the overweight/obese-MAFLD group (aCHR = 1.13; 95% CI = 1.09–1.33; $P < 0.001$). Subgroup analysis and sensitivity analyses using Fine-Gray models and various definitions of MAFLD showed similar trends of the primary result of our study. In the UKB cohort, the DM-MAFLD group also had a higher risk of developing cirrhosis (aHR = 4.21; 95% CI = 3.43–5.16; $P < 0.001$) and hepatocellular carcinoma (aHR = 5.52; 95% CI = 3.40–8.95; $P < 0.001$) than the non-MAFLD group. **Conclusion:** Our study demonstrated a consistent association between MAFLD and the development of liver-related complications, in both our nationwide cohort analysis and among individual's of Caucasian ethnicity. Different subgroups of MAFLD had varying risks of complications, with the DM-MAFLD group showing the highest risk. Stratifying MAFLD patients based on specific criteria representing metabolic disorders may aid in identifying those at a higher risk of liver-related complications. This approach could prove beneficial for screening and surveillance, facilitating early intervention and improved management for patients at an increased risk of liver-related complications.



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2226-A | NAFLD IN PEOPLE WITH HIV EXHIBITS HIGHER FIBROSIS STAGE DESPITE LOWER DISEASE ACTIVITY THAN IN MATCHED CONTROLS

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Background: People with HIV (PWH) are at risk for acute and chronic liver injury including alcohol and metabolic disorders. The morphologic spectrum of non-alcoholic fatty liver disease (NAFLD) and utility of NAFLD activity score (NAS) in predicting fibrosis in PWH remains unknown. In this study, we compared liver histological features of NAFLD in individual's with and without HIV. **Methods:** Two ongoing NIDDK funded observational studies had 123 liver biopsies from PWH with NAFLD (NAFLD-PWH) and 3244 liver biopsies from individual's with NAFLD without HIV. From these datasets, we selected 107 NAFLD-PWH biopsies with 107 age, sex, race/ethnicity, BMI and ALT matched controls (i.e. individual's with NAFLD without HIV). Case and control liver biopsies were centrally read using the NASH CRN histological scoring system. **Results:** NAFLD-PWH were comparable to the control group on age (49 vs 47 y), sex (79% male), race (White 65% vs 61% and African American 13%), ethnicity (Hispanic/Latino 26%), diagnosis of type 2 diabetes (24%), and mean BMI (31 kg/m^2). Compared to the control group, NAFLD-PWH had lower steatosis grade (grades 1 or 2 in 63% cases vs 47% controls, p = 0.01), lower inflammation grade (grades 1 or 2 in 70% cases vs 60% controls, p = 0.03), less hepatocyte ballooning (cases: 61% had none, 15% had many versus controls: 45% had none and 27% had many,

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p = 0.03) and less portal inflammation (8% had more than mild versus 21% of controls). As a result, NAS was lower in NAFLD-PWH (3.17 ± 1.6 vs 3.97 ± 1.59 controls, p < 0.001). There was a trend towards lower steatohepatitis in NALFD -PWH (61%) vs controls (71%, p = 0.09). Conditional multiple logistic regression (Table 1) demonstrated that steatosis (p = 0.02), portal inflammation (p = 0.001) and ballooning (p = 0.01) are less associated with NAFLD-PWH than controls while fibrosis was more associated with NAFLD-PWH than controls (p = 0.03). **Conclusion:** The NAS and histologic drivers of fibrosis (e.g., inflammation and hepatocyte ballooning) are less pronounced in NAFLD-PWH and yet fibrosis stage was generally higher when compared to matched controls with NAFLD but no HIV. This may suggest HIV-specific factors beyond hepatic necroinflammation may contribute to fibrosis in NAFLD-PWH.

Table 1: Conditional logistic regression of NAFLD-PWH versus NAFLD in individuals without HIV on histologic features

	NAFLD-PWH vs. NAFLD in individuals without HIV		
	Odds ratio	95% CI	P
Steatosis grade (0-3)	0.66	(0.46, 0.95)	0.03
Portal chronic inflammation score (0-2)	0.34	(0.18, 0.65)	0.001
Ballooning score (0-2)	0.55	(0.34, 0.88)	0.01
Fibrosis stage (0-4)	1.42	(1.03, 1.97)	0.03

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Jennifer C. Price – Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Abbvie: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Genentech: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; Zydus: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; VIR: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
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2227-A | NAFLD INCREASES THE RISK OF MACE AND REDUCES DISABILITY-FREE SURVIVAL IN OLDER AUSTRALIANS BUT IS NOT AMELIORATED BY ASPIRIN: DATA FROM THE ASPIRIN IN REDUCING EVENTS IN THE ELDERLY (ASPREE) RANDOMISED TRIAL

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Background: Non-alcoholic fatty liver disease (NAFLD) is a significant global health challenge. However, there are limited data on the impact of NAFLD on outcomes in older persons despite a projected doubling of the number of older persons by 2050. Additionally, while some studies suggest NAFLD may increase the risk of major adverse cardiovascular events (MACE) independently of other risk factors, aspirin as primary prevention has not been evaluated. We aimed to assess the impact of NAFLD on MACE and disability-free survival (survival without dementia or persistent physical disability) in community-dwelling older Australians and whether 100mg aspirin ameliorated those risks. **Methods:** We included participants from the ASPREE randomised-controlled trial that enrolled 16,703 community-dwelling Australians aged 70+ years without independence-limiting physical disability, dementia, or cardiovascular disease. Baseline anthropometry, biochemical, and questionnaire data were collected. NAFLD was defined as a Fatty Liver Index (FLI) ≥ 60 in the absence of excess alcohol intake (>14 units/week in women, >21 units/week in men) or steatogenic medications. A FLI of <30 was used as a no-NAFLD comparator. **Results:** 5,967 participants were evaluated (2,970 [49.8%] no-NAFLD vs 2,997 [50.2%] NAFLD, age 75.0 $\pm$ 4.2, 58.9% women). The NAFLD cohort was younger (74.7 $\pm$ 3.9 vs 75.3 $\pm$ 4.4 years, $p<0.001$), heavier (BMI 32.0 $\pm$ 4.0 vs 23.9 $\pm$ 2.4 kg/m^2, $p<0.001$), and had increased rates of

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2247-C | RACIAL DISPARITIES IN PREVALENCE AND INCIDENCE OF CIRRHOSIS AND EXTRAHEPATIC MANIFESTATIONS IN NONALCOHOLIC FATTY LIVER DISEASE

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Background: Nonalcoholic fatty liver disease (NAFLD) has increased in prevalence in recent years. Data on NAFLD in Native Americans are limited. We conducted a study to estimate the prevalence and incidence of NAFLD and its complications in an ethnically diverse population. **Methods:** We conducted a multi-state health system study on NAFLD patients seen at the Banner Health System, representing hospitals across Arizona, California, and Colorado, from 2012 to 2022 using ICD codes. We excluded patients with other causes of liver disease, underweight, baseline decompensated cirrhosis, baseline cancer diagnosis, prior bariatric surgery, or missing data on race, BMI, aspartate and alanine aminotransferase, and platelet. All patients were included in the prevalence cohort, and patients with a follow up of 365 days or greater were included in the incidence cohort. The primary outcomes are the prevalence and incidence of cirrhosis, cardiovascular disease (CVD), metabolic diseases, and chronic kidney disease (CKD) among ethnic groups. We performed a multivariate logistic regression analysis to determine the risk of diseases prevalence and competing risk analysis for diseases incidence among various ethnic groups with NAFLD and adjusted for multiple confounders (Table). Results: We included 51,452 NAFLD patients in the prevalence cohort and 37,027 in the incidence cohort. In both cohorts, 63-64% were White, 28% Hispanic, 3-4% African-American, 2% Native American, and 1% Asian/Pacific Islanders. Compared to White patients, Hispanic patients had a lower prevalence of CVD, and higher prevalence of cirrhosis, higher incidence of mortality, cirrhosis, and liver-related events (LREs). Furthermore, compared to white patients, Native Americans had a higher prevalence of cirrhosis and CKD, with a higher incidence of mortality, LREs, and type II DM. Blacks had a lower prevalence of peripheral artery disease, a higher prevalence of CKD, and a higher incidence of mortality and type II DM. **Conclusion:** In this large, ethnically-diverse cohort of patients with NAFLD, Native American, Hispanic, and Black patients had higher mortality compared to White patients. These same ethnicities had higher incidence of liver-related events and type II DM. Future studies are warranted to understand the underlying reasons for racial disparities in patients with NAFLD.

Table: Logistic regression analysis for race/ethnicity associated with the prevalence of cardiovascular disease, cirrhosis, and chronic kidney diseases among persons with NAFLDa and Competing risk analysis for death and incidence of diseases by race/ethnicity

Prevalence Cohort (n = 51,452)																							
Ethnicity	Any cardiovascular disease		Coronary artery disease		Peripheral artery disease		Cerebrovascular accident		Congestive heart failure		Cirrhosis		Chronic Kidney Disease stage ≥3		Type II DM[*]	
	OR (95% CI)[β]	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
White	Referent		Referent		Referent		Referent		Referent		Referent		Referent		Referent	
Asian / Pacific Islander	**0.76 (0.59-0.98)**	**0.04**	0.81 (0.61-1.07)	0.14	0.89 (0.62-1.29)	0.55	0.98 (0.67-1.43)	0.91	0.80 (0.54-1.17)	0.23	0.85 (0.53-1.38)	0.62	0.97 (0.68-1.37)	0.85	**1.52 (1.08-1.62)**	**<0.01**
Black	1.01 (0.88-1.15)	0.91	1.10 (0.94-1.28)	0.18	**0.72 (0.59-0.89)**	**<0.01**	1.02 (0.85-1.24)	0.81	**1.25 (1.07-1.46)**	**<0.01**	0.73 (0.52-1.03)	0.07	**1.72 (1.47-2.01)**	**<0.01**	**1.98 (1.75-2.21)**	**<0.01**
Hispanic	**0.79 (0.75-0.85)**	**<0.01**	**0.87 (0.81-0.93)**	**<0.01**	**0.83 (0.76-0.90)**	**<0.01**	0.91 (0.83-1.00)	0.05	**0.87 (0.81-0.93)**	**<0.01**	**1.37 (1.21-1.56)**	**<0.01**	**0.86 (0.79-0.94)**	**<0.01**	**1.74 (1.66-1.83)**	**<0.01**
Native American/ Alaskan	0.96 (0.80-1.15)	0.66	0.86 (0.69-1.06)	0.15	**0.57 (0.40-0.80)**	**<0.01**	0.79 (0.57-1.08)	0.14	1.25 (0.997-1.56)	0.05	**2.24 (1.67-2.99)**	**<0.01**	**1.61 (1.28-2.02)**	**<0.01**	**3.48 (3.05-3.96)**	**<0.01**

Incidence Cohort (n = 37,027)												
	Death[†]		Any cardiovascular diseases		Cirrhosis		Liver-related events[‡]		Type 2 Diabetes Mellitus[†]		Major adverse cardiovascular event[‡]	
	HR (95% CI)[β]	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
White	Referent		Referent		Referent		Referent		Referent		Referent	
Asian / Pacific Islander	1.02 (0.46-2.29)	0.96	0.72 (0.47-1.08)	0.11	0.72 (0.23-2.27)	0.58	1.40 (0.82-3.16)	0.17	**1.40 (1.02-2.08)**	**0.04**	**0.59 (0.37-0.83)**	**0.02**
Black	**1.53 (1.08-2.18)**	**0.02**	0.98 (0.80-1.19)	0.82	0.72 (0.40-1.28)	0.26	1.43 (0.98-2.09)	0.07	**1.81 (1.47-2.23)**	**<0.01**	1.04 (0.86-1.25)	0.7
Hispanic	**1.23 (1.02-1.48)**	**0.03**	**0.90 (0.82-0.98)**	**0.02**	**1.35 (1.09-1.67)**	**<0.01**	**1.54 (1.28-1.84)**	**<0.01**	**1.39 (1.26-1.52)**	**<0.01**	**0.88 (0.80-0.96)**	**<0.01**
Native American/ Alaskan	**2.46 (1.58-3.84)**	**<0.01**	1.13 (0.87-1.48)	0.36	1.67 (0.95-2.95)	0.08	**1.99 (1.24-3.18)**	**<0.01**	**1.83 (1.49-2.48)**	**<0.01**	1.14 (0.88-1.50)	0.32

Abbreviations: CI, confidence interval; OR, odds ratio; HR, hazard ratio
[β]OR adjusted for age, sex, race, smoking status, hypertension, dyslipidemia, DM, and aspirin and statin use.
[*]For Type II DM, OR was adjusted with the same confounders excluding DM
[†]Cox proportional hazards model was performed for death analysis.
[‡]Liver-related events are defined as incidence of ascites, variceal bleeding, hepatic encephalopathy or hepatocellular carcinoma
[§]For type 2 diabetes mellitus, HR was adjusted with the same confounderss excluding type 2 diabetes mellitus.
[¶]Major adverse cardiovascular event defined as incidence of coronary artery disease, cerebrovascular disease, congestive heart failure, or all cause mortality
[#]HR adjusted for age, sex, race, smoking status, hypertension, dyslipidemia, DM, and aspirin and statin use.

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2248-C | REGIONAL AND SEX DIFFERENCES IN INCIDENCE OF ADVERSE CLINICAL EVENTS IN PERSONS WITH NAFLD: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Nonalcoholic fatty liver disease (NAFLD) incidence and prevalence varies by region. We aimed to determine the regional incidence rates of adverse clinical events associated with NAFLD. **Methods:** We performed a systematic review and meta-analysis of cohort studies of adults with NAFLD at baseline using 3 databases (Cochrane library, EMBASE, PubMed) to evaluate the pooled incidence of adverse clinical events associated with NAFLD. Random-effects models were used to estimate the pooled incidence of adverse clinical events. **Results:** A total of 75 eligible studies (1,375,554 persons) were included. The included regions were North America (n = 16 studies, 563037 persons), Europe (n = 25, 498467 persons), and Western Pacific/Southeast Asia (WPSEA) (n = 34, 314050 persons). Median study year and person-years follow up are as follows: North America (2007, 5466 person-years), Europe (2007, 5400 person-years), WPSEA (2007, 5533 person-years). No asymmetry was observed on funnel plot analysis, with egger's test showing no significant differences for all outcomes ($p > 0.05$). All analyses showed significant heterogeneity ($I^2 \geq 50\%$). Data are reported as incidence rate per 1000 person-years. All-cause, cardiovascular disease (CVD)-related, and non-liver cancer related mortality were lowest in WPSEA and highest in Europe. No significant differences were observed in liver-related mortality by region. Incidence rates of liver transplant were highest in North America and lowest in Europe. Hepatocellular carcinoma (HCC) had the highest incidence rate in WPSEA and lowest in North America. No significant differences were noted in the incidence rate of decompensated cirrhosis. Europe the lowest incidence of hypertension and type 2 diabetes, with North America having the highest incidence of hypertension and WPSEA having the highest incidence of type 2 diabetes. Overall incidence of cardiovascular events was highest in NA and lowest in WPSEA. Individual cardiovascular events (coronary artery disease/congestive heart failure, myocardial infarction, and stroke) showed no significant differences between regions along with renal impairment (table). No significant differences were observed in the incidence rate of adverse events when comparing males and females: all-cause mortality (12.5 vs 8.79, p = 0.62), liver-related events (48.4 vs 49.6, p = 0.96), decompensated cirrhosis (37.4 vs 32.8, p = 0.54), HCC (3.5 vs 11.1, p = 0.37), fibrosis progression (48.9 vs 52.1, p = 0.87), CVD (30.8 vs 30.8, p = 0.99), type 2 diabetes (23.5 vs 22.3, p = 0.81), and non-liver cancer (10.7 vs. 7.6, p = 0.41). **Conclusion:** Geographical variations in the incidence of adverse clinical events were observed among those with NAFLD. Additionally, no significant differences in adverse event were observed by sex. A multidisciplinary team should be considered in the management of NAFLD patients to treat and prevent the multitude of complications associated with NAFLD.

	Incidence rate per 1,000 person-years			
	Europe	North America	Western Pacific/ Southeast Asia	p-value
All-cause mortality	19.34 (13.01-25.67)	14.99 (8.86-21.12)	7.54 (3.49-11.60)	0.0026
CVD-related mortality	7.01 (4.19-9.98)	5.22 (1.65-8.78)	1.30 (0.54-2.05)	<0.0001
Non-liver cancer mortality	4.79 (2.53-7.06)	2.80 (2.49-3.10)	1.65 (0.82-2.49)	<0.0001
Liver-related mortality	2.13 (1.53-2.72)	2.47 (0.00-4.98)	2.80 (0.68-4.93)	0.82
Non-liver cancer	12.55 (11.93-13.18)	16.62 (15.32-17.93)	7.49 (6.87-8.11)	<0.0001
Liver-related events	28.58 (6.35-50.80)	32.12 (4.19-60.06)	12.41 (3.01-21.81)	0.22
Fibrosis progression	50.85 (32.65-69.04)	50.66 (0.00-104.73)	51.33 (0.00-118.10)	0.99
Cirrhosis	10.86 (5.52-16.19)	5.10 (2.23-7.97)	9.46 (0.00-20.23)	0.15
Liver transplant	1.85 (0.00-4.33)	25.36 (0.00-74.07)	9.11 (3.73-14.50)	0.038
HCC	2.39 (1.01-3.77)	0.37 (0.30-0.46)	4.08 (1.83-6.34)	0.0001
Cirrhotic decompensation	10.13 (4.28-15.99)	5.32 (0.16-10.48)	11.35 (0.00-25.15)	0.42
Ascites	6.40 (0.00-12.81)	2.25 (0.58-3.93)	7.31 (0.00-19.13)	0.35
Varices	1.95 (0.30-3.59)	3.51 (0.00-7.48)	4.31 (0.57-8.06)	0.45
Hepatic encephalopathy	3.66 (0.45-6.87)	1.56 (0.68-2.43)	3.85 (0.00-9.16)	0.34
Hypertension	12.98 (4.13-21.84)	43.04 (34.34-51.74)	36.57 (17.31-55.84)	<0.0001
Dyslipidemia	22.00 (0.00-60.45)	21.16 (0.00-47.63)	39.08 (23.59-54.56)	0.43
Type 2 diabetes mellitus	14.31 (10.34-18.27)	19.90 (6.63-33.17)	22.88 (17.23-28.54)	0.048
Cardiovascular events	20.47 (9.52-31.43)	23.05 (6.43-39.67)	5.09 (1.25-8.94)	0.0059
Coronary artery disease/congestive heart failure	37.58 (1.49-73.68)	11.48 (0.00-24.32)	N/A	0.18
Myocardial infarction	2.57 (1.76-3.38)	3.52 (1.10-5.94)	0.87 (0.00-2.30)	0.073
Stroke	4.45 (3.49-5.41)	6.45 (2.35-10.55)	N/A	0.35
Renal impairment	14.21 (7.98-20.45)	8.20 (7.99-8.41)	6.62 (2.80-10.44)	0.12

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2249-C | RELATIONSHIP BETWEEN LIPOPROTEINS AND LIVER ENZYMES IN A PRIMARY CARE AND ENDOCRINOLOGY COHORT OF 246,252 PATIENTS

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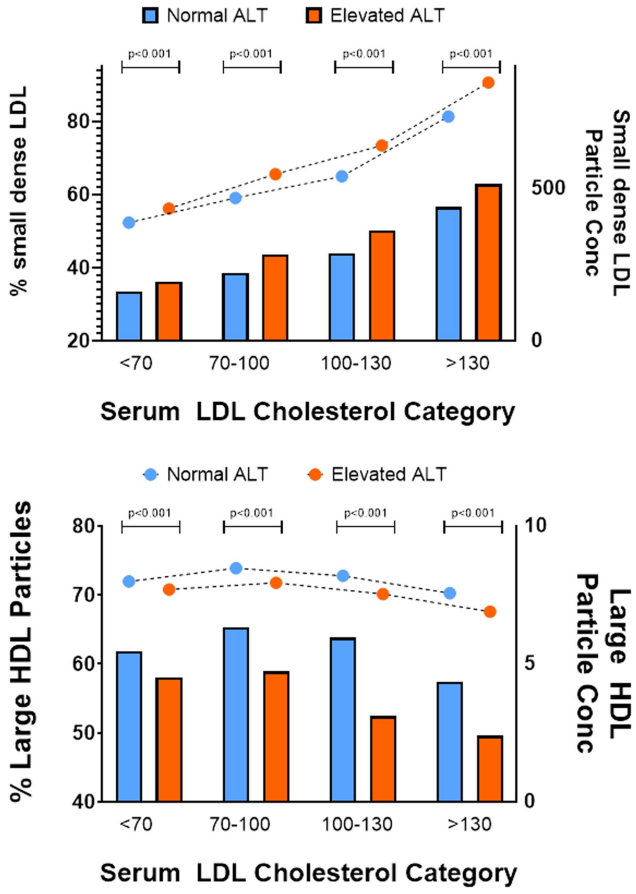
Background: Liver plays a central role in lipoprotein metabolism and is a key driver of atherogenesis. This relationship is best described in patients with non-alcoholic fatty liver disease (NAFLD) where cardiovascular disease is the leading cause of mortality. The published literature evaluating atherosclerosis in liver disease suffers from relatively small sample size and ascertainment bias, thus, limiting their interpretation on a larger scale such as primary care. Therefore, the aim of the current study was to better delineate the relationship between serum atherogenic risk and liver disease in a large primary care cohort. **Methods:** This retrospective study used anonymized Labcorp data of adult patients who had blood testing mostly in a primary care setting from Feb 2021 to Feb 2023. Atherogenic risk was quantified via NMR-based measurements of LDL, VLDL and HDL particle concentrations. To better understand the relationship between LDL-C based goals and atherogenic risk, the cohort was divided into LDL-C based targets (LDL < 70, 70-100, 100-130, and > 130 mg/dL). Liver disease was defined as elevated ALT (> 19 and > 31 IU/L in women and men, respectively). As cirrhosis and alcohol use can affect lipoprotein metabolism, a sensitivity analysis was performed where patients with ALT:AST < 1 were excluded. **Results:** A total of 246,252 patients met entry criteria (n = 80,848 with elevated ALT). Serum atherogenic lipoprotein concentrations (large VLDL, small LDL, and HDL particles) were significantly higher among patients with elevated ALT. Across the LDL-C thresholds, patients with elevated ALT had more atherogenic lipoproteins characterized by higher concentrations of pro-atherogenic small dense LDL and large VLDL particles and reduced levels of anti-atherogenic HDL particles (Figure 1; bar and line graphs represents % absolute values, respectively). A stepwise increase in the atherogenic profile was noted from lowest to highest LDL category, which were further exacerbated in patients with elevated ALT. In sensitivity analysis (excluding patients with ALT:AST < 1), the relationship between elevated ALT levels and higher concentrations of pro-atherogenic and lower concentrations of anti-atherogenic lipoproteins was re-demonstrated. **Conclusion:** In a large, community-based cohort, elevation in liver enzymes was closely associated with a more pro-atherogenic lipoprotein profile. These findings persisted in sensitivity analysis, suggesting these findings are likely related to underlying NAFLD.



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2250-C | RELATIONSHIP OF BODY MASS INDEX TO INCIDENT MAJOR ADVERSE CARDIOVASCULAR EVENTS AND INCIDENT LIVER-RELATED OUTCOMES IN PATIENTS WITH BIOPSY-PROVEN NONALCOHOLIC FATTY LIVER DISEASE

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Background: NAFLD in nonobese individual's is increasingly recognized, and its outcomes are not well-defined. We sought to compare rates of incident major cardiovascular events (MACE) and liver-related outcomes in patients with biopsy-proven NAFLD of varying body mass index (BMI) in a hospital network-based cohort. **Methods:** We identified all adults with biopsy-confirmed NAFLD in the Mass General Brigham health network, between 1999 and 2021, using a validated natural language processing (NLP) algorithm. BMI was categorized into nonobese (BMI < 30), World Health Organization (WHO) class I obesity (BMI 30-34), and WHO class II/III obesity (BMI ≥ 35). Outcomes were defined by ICD-9/ICD-10 codes and included incident MACE (composite hospitalization for myocardial infarction, heart failure, cerebrovascular disease, or peripheral vascular disease) and incident liver-related events (cirrhosis, hepatocellular carcinoma, or advanced liver disease). Cox proportional hazards models were used to estimate multivariable-adjusted hazard ratios (aHRs) and 95% confidence intervals (CI) for study outcomes, accounting for age, sex, diabetes, hypertension, aspirin use, statin use, liver fibrosis stage, and smoking status. **Results:** Among 1624 patients included in the study, 54% were female, with mean age 48 and mean BMI 31.5 kg/m^2; 53% had nonalcoholic steatohepatitis (NASH) on liver biopsy. Compared to the nonobese reference group, we observed significantly higher rates of incident MACE in patients with class 1 obesity (aHR 1.34, 95% CI 1.05-1.72), and in those with class II/III obesity (aHR 1.34, 95% CI 1.02-1.77). In subgroup analyses, the excess CVD risk associated with obesity was most pronounced in patients with NASH, compared to the nonobese reference group (class I obesity aHR 1.73, 95% CI 1.20-2.48; class II/III obesity aHR 1.59, 95% CI 1.08-2.34). In contrast, among patients without NASH, no significant differences in risk of MACE were found across BMI categories. There was no difference in rates of liver-related outcomes, including cirrhosis, hepatocellular carcinoma, and advanced liver disease according to BMI category. **Conclusion:** In a large cohort with biopsy-proven NAFLD, obesity was significantly associated with

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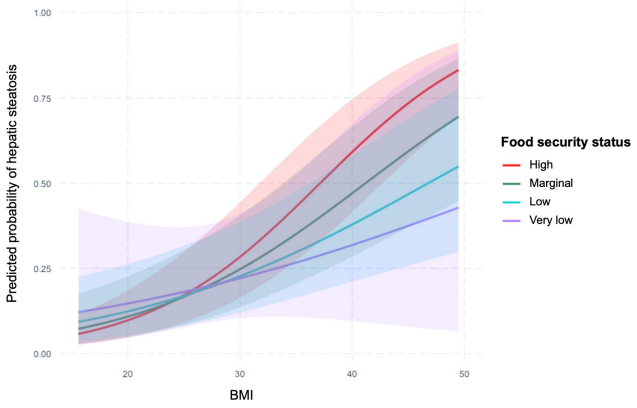
of women with and without HIV, women who reported food insecurity with BMI < 25 kg/m^2 had higher odds of hepatic steatosis while women with BMI ≥ 25 kg/m^2 had lower odds of hepatic steatosis. Our findings suggest that food insecurity, in the presence of other factors that might lower BMI, such as chronic inflammatory processes, could worsen hepatic steatosis whereas food insecurity may attenuate the effect of higher BMI on hepatic steatosis. This study lays the groundwork for future efforts exploring potential mechanistic pathways.



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2258-C | THE CASCADE OF NAFLD CARE IN THE VA: A WINDOW OF OPPORTUNITY

Sebastian Niezen[1], Heather M. Patton[2], Timothy R. Morgan[3], Jasmohan S. Bajaj[4], Dawn Scott[5], Vera Yakovchenko[6], Yiwen Yao[7], Lauren A. Beste[8,9] and Shari S. Rogal[6,10], (1)University of Pittsburgh Medical Center, (2)VA San Diego Healthcare System, (3)VA Long Beach Healthcare System, (4)Virginia Commonwealth University and Central Virginia Veterans Healthcare System, (5)Central Texas VA Healthcare System, (6)VA Pittsburgh Healthcare System, (7)VA Salt Lake City Healthcare System, (8)VA Puget Sound Healthcare System, (9)University of Washington, (10)University of Pittsburgh

Background: Non-alcohol-related fatty liver disease (NAFLD) affects over one-third of the U.S. population. Yet, it remains challenging to identify patients most at risk for disease progression. As pharmacotherapies emerge, it is critical to understand the cascade of NAFLD diagnosis and care to maximize the benefits of and access to these agents. The aims of this evaluation were to 1) develop a VA cascade of NAFLD care and 2) assess the current management of NAFLD in the VA. **Methods:** Using the Corporate Data Warehouse, we identified Veterans with labs or ICD-10 diagnosis codes for NAFLD risk factors (i.e., obesity, diabetes, prediabetes, or dyslipidemia) from 2019 to 2022. We collected demographic characteristics, comorbidities, Fibrosis 4 index score (FIB-4), diagnosis of NAFLD or cirrhosis, use of VA weight loss programs, GLP1-RA prescription, and GI/ hepatology visits and used regression models to identify the factors associated with diagnosis codes for NAFLD or cirrhosis diagnosis and GI/hepatology visits. **Results:** 4,230,277 Veterans had NAFLD risk factors, among whom 6% had FIB-4 > 2.67, 5% had a NAFLD diagnosis; and 2% had a cirrhosis diagnosis. The ratio of NAFLD: cirrhosis diagnoses was 3:1, suggesting a large undiagnosed population. Factors significantly associated with documented NAFLD diagnosis included higher FIB-4, younger age, female sex, elevated ALT, metabolic comorbidities, and alcohol use disorder. Within the cohort, 252,048 (6%) were engaged with a VA weight loss program, 104,120 (3%) received a GLP1-RA prescription, and 371,217 (9%) were seen in GI/ hepatology. Having a NAFLD diagnosis was associated with significantly increased use of VA weight loss programs (5.3% vs. 12.5%, $p < 0.001$) and GI/hepatology visits (7.6% vs. 31.5%, $p < 0.001$). **Conclusion:**

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Nearly half of Veterans in VA care have risk factors for NAFLD and 6% have a high FIB-4. However, few are diagnosed with NAFLD or cirrhosis, indicating opportunities to identify additional cases of NAFLD. NAFLD and cirrhosis diagnoses were associated with engagement with VA weight loss program and GI/hepatology engagement. These data suggest the need to efficiently diagnose and triage the large number of people with NAFLD risk factors to ensure appropriate care, particularly with the emergence of new pharmacotherapies.

Table 1. Patient characteristics at risk of NAFLD in VA

	Total number of Veterans at risk for NAFLD	FIB-4<1.3	FIB-4 1.3-2.67	FIB-4>2.67	GI/Hepatology visit	Elevated ALT	GLP1-RA Prescription
	N = 4,230,277	N=1,716,729	N=1,538,466	N=247,733	N = 371,217	N = 760,484	N = 104,120
Diabetes	1,946,846 (46.0%)	784,694 (45.7%)	703,772 (45.7%)	117,259 (47.3%)	179,462 (48.3%)	358,583 (47.2%)	103,055 (99.0%)
Obesity	2,002,969 (47.3%)	898,496 (53.1%)	677,127 (44.7%)	88,437 (36.3%)	206,222 (55.6%)	477,423 (62.8%)	67,962 (65.3%)
Hyperlipidemia	2,659,462 (62.9.6%)	1,059,304 (62.7%)	1,043,963 (68.9%)	151,363 (62.1%)	253,817 (68.4%)	484,205 (63.7%)	74,666 (71.7%)
NAFLD diagnosis	207,529 (4.9%)	69,590 (4.1%)	68,491 (4.5%)	17,557 (7.2%)	57,126 (15.4%)	104,826 (13.8%)	9,252 (8.9%)
Cirrhosis diagnosis	86,092 (2.0%)	9,118 (0.5%)	22,289 (1.5%)	27,598 (11.3%)	36,073 (9.7%)	28,837 (3.8%)	2,933 (2.8%)

Data are presented as n (%)

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2259-C | THE GLOBAL SURVEY OF DISEASE BURDEN AND STIGMA AMONG PATIENTS WITH NAFLD AND THEIR HEALTHCARE PROVIDERS

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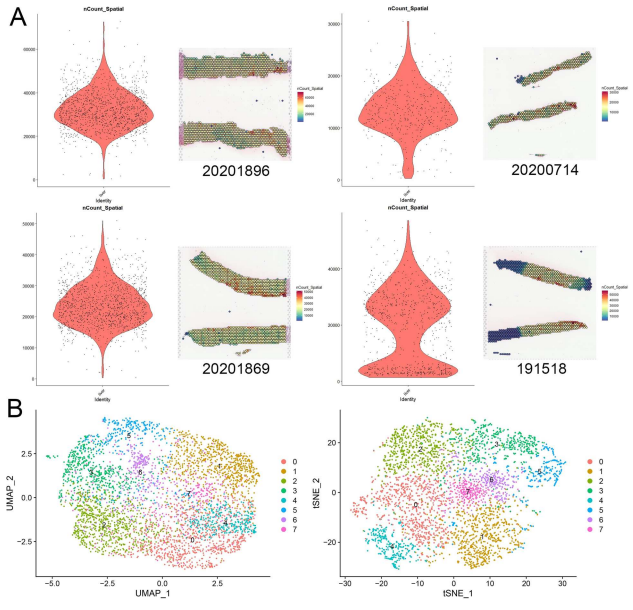
Symbols: ♦, Poster of Distinction; ★, Foundation Award Recipient

suggested that differentially expressed genes of cluster5 were concentrated in ECM structural components and signalling molecules. Six cell types were obtained by integrating the single-cell sequencing dataset (GSE189175). Compared with the healthy control and NAFL groups, the NASH group had significantly increased proportions of HSCs and myofibroblasts, which were distributed in the lobule and the portal area around the fibrotic area. Simultaneously, the infiltration of Kupffer cells around the fibrotic area also increased. The cell communication analysis showed that diffusive cell communication was the main type, including endocrine, paracrine and autocrine communication, followed by ECM-receptor cell communication. According to the analysis of differentially expressed genes in the subsets, AEBP1 and DPT are relatively highly expressed in cluster5, as well as in HSCs and myofibroblasts. SCENIC analysis found that AEBP1+ and DPT+ myoblasts were involved in the activation of HSCs and fibrosis formation. Immunohistochemistry verified the high expression of AEBP1 and DPT in patients with NASH fibrosis. After transfection of AEBP1 and DPT interference fragments in LX2 cells in vitro, the mRNA level of Collagen I in cells was significantly lower than that of the siRNA-NC group and blank control group. **Conclusion:** Our study is the first to reveal lineage-specific changes in gene expression, subpopulation composition and cell communication in NASH fibrosis, providing new directions for potential therapeutic targets for NASH fibrosis.



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2371-C | StarD5 LEVELS OF EXPRESSION CORRELATE WITH ONSET AND PROGRESSION OF NASH LIVER FIBROSIS

Daniel Rodriguez-Agudo[1], Genta Kakiyama[2], Nanah Bai-Kamara[3] and William M. Pandak Jr[1], (1)Virginia Commonwealth University, (2)Mcguire Veterans Affairs Medical Center, (3)VA Hospital

Background: Steroidogenic acute regulatory lipid transfer protein 5 (**StarD5**) transfers cholesterol to the plasma membrane (PM) in response to endoplasmic reticulum (ER) stress, preventing ER cholesterol accumulation. In addition to known decreases in PM cholesterol and altered PM fluidity, its knockout increases liver triglyceride levels; suggesting an unappreciated physiologic function. We attempted to further characterize StarD5 functions to determine why. **Methods:** livers from wild type (WT) mice and StarD5$^{-/-}$ fed a normal or a western diet were analyzed for protein expression by immunoblot, cholesterol, cholesterol metabolites and triglyceride levels, while blood was analyzed for glucose and insulin levels. Total RNA was isolated from WT and StarD5$^{-/-}$ mice for RNAseq and for a fibrosis gene expression panel. VLDL secretion levels were determined in wild type and StarD5$^{-/-}$ mice following tyloxapol injection. Fibrosis was determined by Masson's Trichrome staining of livers from WT and StarD5$^{-/-}$ mice fed a western diet. Rescue experiments were performed in StarD5$^{-/-}$ hepatocytes with an ADV-StarD5 and in StarD5$^{-/-}$ mice with an AAV9-StarD5 to determine reversal of the phenotype. **Results:** In addition to increased hepatic triglyceride/cholesterol levels, global StarD5 knockout (StarD5$^{-/-}$) mice displayed reduced plasma triglycerides and liver VLDL secretion as compared with wild type (WT) counterparts. Elevated Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score demonstrated insulin resistance (IR). Interestingly, decreased hepatic StarD5 expression was found in WD-fed WT mice. WD-fed StarD5$^{-/-}$ mice up-regulated the transcriptional regulator Taz expression with accelerated liver fibrosis. Impaired oxysterol 7α-hydroxylase (Cyp7b1) protein coupled with accumulated toxic cholesterol metabolites (oxysterols) correlated with presentation of fibrosis. Oxysterol responsive protein levels including fatty acids synthetase (Fas) and Acetyl CoA-carboxylase (Acc) were correlated with increased *Srebp-1* mRNA levels in the StarD5$^{-/-}$ mice liver. In the gain-of-function study, AAV9-mediated hepatocyte selective StarD5 overexpression led to reduced hepatic triglycerides, and improved HOMA-IR scores in StarD5$^{-/-}$ mice. The impaired hepatic StarD5 and Cyp7b1 with elevated oxysterol were found in two additional mouse models of fibrosis and human NASH livers. **Conclusion:**

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

Downregulation of StarD5 with hepatic lipid excess is an unappreciated key physiologic function directing lipid storage for future needs. Conversely, impaired StarD5 with prolonged lipid/cholesterol excess initiates/accelerates fatty liver's transition to fibrosis; mediated via dysregulation in the oxysterol signaling pathway.
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2372-C | STATINS IMPROVE LIVER FUNCTION AND MINIMIZE THE DEGREE OF LIVER DAMAGE BY MODULATING CELL DEATH

Alejandro H. Gutierrez[1], Zheng Kang[1], Zoe Boyer-Diaz[2], Arantza Lamas Paz[1], Javier Vaquero[3,4], Rafael Bañares[3,4], Jaime Bosch[2,4,5], Jordi Gracia-Sancho[2,4,5], Jonel Trebicka[6,7], Yulia Nevzorova[1,3,4], Carlos Sanz-García[1] and Francisco Javier Cubero[1,3,4], (1) Complutense University School of Medicine, (2)Idibaps, (3)Instituto De Investigación Sanitaria Gregorio Marañón (IiSGM), (4)Centro De Investigación Biomédica En Red De Enfermedades Hepáticas y Digestivas (CIBEREHD), (5)University of Bern, (6) University Clinic Frankfurt, (7)European Foundation for the Study of Chronic Liver Failure and Grifols Chair, Barcelona, Spain

Background: Patients with advanced liver fibrosis are frequently treated with statins. However, how statins modulate liver cell function remains elusive. In the present work, we hypothesized that statins can modulate cell death, thereby ameliorating advanced chronic liver failure (ACLF). **Methods:** Carbon tetrachloride (CCl4) was used to induce liver fibrosis in Wistar and Sprague Dawley rats and rodents were treated with Simvastatin and Atorvastatin, respectively. After sacrifice, qRT-PCR, Western blot, and IF analysis were performed. Functional experiments were carried out with a human hepatocyte cell line (HepG2), and primary isolated hepatocytes from cirrhotic patients, treated with TNF/D-GalN in the presence or absence of statins. Finally, Western blot and qPCR analysis were performed in liver biopsies of twelve obese patients following bariatric surgery with NAFLD activity scores (NAS) ranging from 0 to 3, and a microarray analysis of ACLF patients was examined. **Results:** Cell death markers of apoptosis and necroptosis (phospho-MLKL and cleaved caspase 3 (CC3)) were overexpressed in liver extracts of patients with higher NAS scores and ACLF. Statins reduced CCl_4-induced overexpression of markers of liver fibrosis and inflammation, and apoptosis in animals with ACLF, thereby attenuating the expression of CC3, CC8 and TUNEL-positive cells. Moreover, statins therapy protected both HepG2 cells and cirrhotic primary hepatocytes from acute -induced cell death. **Conclusion:** Statin therapy enhanced liver function and reduced systemic inflammation in human cell lines and rat models of ACLF, thereby mitigating the severity of the condition. We describe a novel mechanism by which statins specifically protected against cell death.
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2373-C | SUBCELLULAR DISPOSITION OF ADENOSINE A3 RECEPTOR IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE: INSIGHTS INTO INTRANUCLEAR TRANSLOCATION

Huiyul Park[1], Sang Bong Ahn[2], Eileen Yoon[3], Hyunwoo Oh[4], Hyo Young Lee[4], Joo Hyun Sohn[3] and Dae Won Jun[3], (1)Hanyang University, (2)Eulji Medical Center, (3) Hanyang University College of Medicine, (4)Uijeongbu Eulji Medical Center

Background: Recent studies have shown decreased expression of adenosine A3 receptor (A3AR) in the liver of patients with non-alcoholic fatty liver disease (NAFLD), suggesting its potential involvement in NAFLD pathogenesis. However, the significance and role of intranuclear translocation of A3AR have not been thoroughly investigated. Thus, the aim of this study was to explore the differences in A3AR expression between NAFLD patients and healthy controls, specifically focusing on its subcellular distribution. **Methods:** A total of 163 NAFLD cohorts (Control: n = 61, NAFLD: n = 76, NASH: n = 26) were examined to compare A3AR expression in liver tissue and peripheral blood mononuclear cells (PBMCs). Immunofluorescence expression and cell fractionation techniques were utilized to analyze the subcellular distribution of A3AR following treatment with palmitic acid (PA) and oleic acid (OA). **Results:** Analysis of in-house and public RNA sequencing data revealed no significant differences in A3AR expression between healthy controls and NAFLD patients. Consistently, A3AR expression in PBMCs

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2377-C | THE CERAMIDE SYNTHASE (CERS) FAMILY AND RELATED LNCRNAS CONTRIBUTING TO NASH-HCC DISEASE PROGRESSION

Jing Zeng[1,2], Derrick Zhao[1], Yunling Tai[1], Lianyong Su[1], Xixian Jiang[1], Xuan Wang[1], Emily Gurley[1], Phillip B. Hylemon[1], Jiangao Fan[2], Sayed Obaidullah Aseem[3], Arun Sanyal[3] and Huiping Zhou[1], (1)Department of Microbiology and Immunology, Medical College of Virginia and Mcguire Veterans Affairs Medical Center, Virginia Commonwealth University, Richmond, VA, (2) Department of Gastroenterology, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China, (3)Department of Internal Medicine and GI Division, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298, USA

Background: Nonalcoholic fatty liver disease (NAFLD) is the fastest-rising cause of end-stage liver disease for liver transplantation. The underlying mechanisms of NAFLD progression from nonalcoholic steatohepatitis (NASH) to hepatocellular carcinoma (HCC) remain unclear. Ceramide synthases (CERSes) have been implicated in the pathogenesis of NASH-HCC. Ceramide is a key mediator of lipotoxicity in NASH. Long non-coding RNAs (lncRNAs) are important regulators in gene expression related to tumorigenesis. However, the specific roles of the CERSes and CERS-related lncRNAs (CERSRLs) in NASH-HCC development remain unknown and is the focus of this study. **Methods:** RNAseq data of HCC patients were obtained from The Cancer Genome Atlas (TCGA) database. Co-expression analysis was performed to identify CERSRLs in differentially expressed (DE) lncRNAs. Prognostic CERSRLs were selected using univariate Cox analysis, and a prognostic model was constructed. Model validation was performed using Kaplan-Meier curves based on risk scores. In separate study, DIAMOND NASH mouse model was used. Male mice (21-24 weeks old) were fed with Western diet and a high fructose-glucose water (WDSW) or chow diet ad libitum for 6 months or 1 year. The hepatic RNA transcriptome was analyzed using RNAseq. CrossMap was used to identify mouse CERSRLs based on human CERSRLs with Ensembl and NONCODE databases. Ceramide profiles in the serum and liver were quantified using LC-MS/MS. **Results:** CERSes were significantly upregulated in human HCC compared to healthy controls in TCGA. CERS1, CERS5, and CERS6 exhibited prognostic significance. Co-expression analysis identified 122 DE CERSLs, of which 23 were survival-related. A prognostic signature consisting of 6 CERSLs was constructed, with worse HCC prognoses in the high-risk group. In mouse model, all mice developed NASH and HCC after feeding with WDSW for 6 months and 1 year, respectively. We identified 110 potential mouse CERSLs. In both human HCC and mouse NASH-HCC, 3 DE CERSLs were identified as potential candidates for NASH and HCC, including 2 upregulated (Gad1os and Norad) and 1 downregulated Gm14164, compared to the controls in mice. LC-MS/MS data showed significant changes in ceramide profiles in NASH and HCC. **Conclusion:** Our study provides insights into the association between the CERSes and CERSRLs in the progression of NASH and HCC. Further research is needed for the potential application of CERSRLs as diagnostic or prognostic markers in the clinic. Keywords: non-alcoholic steatohepatitis; hepatocellular carcinoma; CERS; ceramide; lncRNA

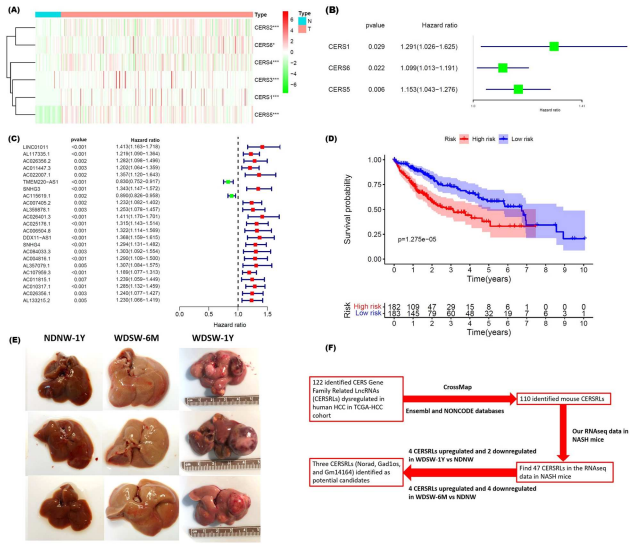

Fig.1 (A) Heatmap of the CERSes in TCGA-HCC. **(B)** CERS1, CERS5, and CERS6 exhibited prognostic significance. **(C)** 23 of 122 DE CERSL identified by co-expression analysis were survival-related. **(D)** A prognostic signature consisting of 6 CERSLs was constructed, with worse HCC prognoses in the high-risk group. **(E)** Liver images of mice developed NASH and HCC after feeding with WDSW for 6 months and 1 year, respectively. **(F)** A Flowchart of this study.

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2378-C | THE EFFECT OF GLYCINE ON PHOSPHOLIPIDS / SPHINGOLIPIDS COMPOSITION DURING HEPATO-CARCINOGENESIS IN HEPATOCYTE-SPECIFIC PTEN KNOCKOUT MICE

Kazuyoshi Kon[1], Hyeon-Cheol Lee-Okada[2], Kumiko Arai[1], Akira Uchiyama[1], Toshifumi Sato[1], Hiroo Fukada[1], Takehiko Yokomizo[2] and Kenichi Ikejima[1], (1) Juntendo University School of Medicine, (2)Juntendo University Graduate School of Medicine

Background: Phospholipids and sphingolipids are constituents of cell membranes, act as mediators, and are involved in various liver diseases including steatohepatitis. However, changes in these lipids during steatohepatitis-associated hepatocarcinogenesis are unknown. Here, we clarified changes in phospholipids and sphingolipids in the process from steatohepatitis to hepatocarcinogenesis by lipidomic analysis using hepatocyte-specific phosphatase and tensin homolog deleted from chromosome 10 (PTEN) knockout mice, and further analyzed the effects of administration of the amino acid glycine on lipid composition. **Methods:** Male Alb-Cre TG (+) PTEN$^{flox/flox}$ mice (PTEN KO) aged 11-17 weeks were fed a normal diet or a diet containing 5% glycine for 2 or 24 weeks. Wild-type or TG (-) mice fed a normal diet were used as control. The number of liver tumors with a diameter of 2 mm or more was counted. Hepatic lipid composition was comprehensively analyzed using liquid chromatography coupled to tandem mass spectrometry. **Results:** PTEN KO developed severe steatohepatitis, whereas 2-weeks administration of glycine improved steatohepatitis and significantly reduced serum AST and ALT levels. Lysophosphatidylcholine (LPC) 16:0, 18:2, 18:0, and 22:6 were significantly lower in liver tissue from PTEN KO, and glycine

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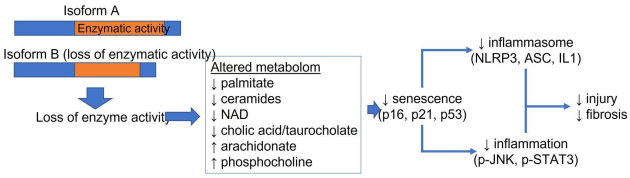
liver fibrosis was strongly reduced in Lrat$^{\Delta Serpine1}$ mice (vs Serpine1$^{flox/flox}$ mice). **Conclusion:** Human liver spheroids serve as a useful tool to study NASH in a dish. Although SERPINE1 is expressed in different cell populations, our findings in human spheroids and HSC-specific Serpine1 knockout mice suggest that SERPINE1 in HSCs can become a target for anti-fibrotic therapy.
Disclosures: The following people have nothing to disclose: Hyun Young Kim, Wonseok Lee
Disclosure information not available at the time of publication: Cuijuan Han, Sara Brin Rosenthal, Xiao Liu, Haeum Jang, Karin Diggle, Tatiana Kisseleva, David A. Brenner

2385-C | THE rs72613567:TA SPLICE VARIANT OF HUMAN HSD17B13 REDUCES HEPATIC INFLAMMAGING TO AMELIORATE NONALCOHOLIC STEATOHEPATITIS AND FIBROSIS

Arun Sanyal[1], Mulugeta Seneshaw[2], Hae-Ki Min[2], Faridoddin Mirshahi[1], Michael Idowu[2], Prakash Ramachandran[3], John Min[2], Huiping Zhou[2], Siddharth Ghosh[2], Lauren Cowart[2], Yang Yue[2], Ekaterina Smirnova[4], Amon Asgharpour[5], Mohammad S. Siddiqui[2], Fadi N. Salloum[2] and Patricia J. Sime[2], (1) Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA, (2) Virginia Commonwealth University, (3)Edinburgh University, (4)Virginia Commonwealth University, Richmond, VA, (5)Virginia Commonwealth University Health System

Background: The hydroxysteroid dehydrogenase 17 B13 isoform B (rs72613567) (HSD^B) confers protection from NASH and fibrosis. The underlying mechanisms are not known. AIMS: (1) To determine if the HSD splice variant (HSD^B) decreases fibrosis in the diet-induced animal model of NAFLD (DIAMOND^{TM}) mice, (2) To determine the impact of HSD^B on NASH-related mechanistic pathways **Methods:** NASH was induced by a high-fat diet with adlib sugar water (Western Diet (WD)). Liver targeted delivery of luciferase (negative control), HSD isoform A (HSD^A) or HSD^B was achieved using TBG-AAV vectors. Liver histology was assessed by H&E Sirius Red. The hepatic metabolome was interrogated using GCMS and LCMS. Gene expression was quantified by mRNA qPCR and protein expression by Western blot. **Results:** A total of 10 mice each on WD were randomly assigned to receive AAV-luc, AAV-HSD^A or AAV-HSD^B. Mice on chow diet (CD) were healthy controls. After 16 weeks on the diet, liver-specific expression of HSD was confirmed by qPCR and Western blot. *(A) Histology:* Mice on CD had normal histology. AAV-luc on WD developed steatohepatitis with stage 1-2 fibrosis as did AAV-HSD^A. In contrast, AAV-HSD^B only had steatosis with minimal or no fibrosis. *(B) Chemistry:* WD increased AST and ALT in AAV-luc and HSD^A; this was significantly abrogated by HSD^B. *(C) Metabolomics:* Compared to AAV-luc and HSD^A, HSD^B mice on WD had lower palmitate, 18:0 containing ceramides, reduced cholic acid and its derivatives, lower phosphocholine and higher arachidonic acid and anabolic profile (higher ketoglutarate:citrate). *(D) Molecular signaling:* WD increased de novo lipogenic gene expression along with ER stress, oxidative stress, autophagy, senescence, inflammation and fibrosis signaling in AAV-luc and HSD^A. In contrast, HSD^B decreased ($p < 0.05$ for all) senescence (p16, p21, p53) and downstream activation of inflammasome (ASC, NLRP3, Caspase-1, IL1-β), inflammatory- (p-JNK) and proliferative-signaling (p-ERK). Ceramide synthetase 1, 6 and the oxidative marker nrf2 was decreased in HSD^B. While GP130 was increased in all groups on WD, downstream p-STAT3 (Y705) but not (S727) was markedly suppressed in HSD^B. WD-induced fibrogenic drive (TGF-β, procollagen 1 and 3 and α-smooth muscle actin) was significantly decreased by HSD^B. **Conclusion:** The splice variant B of HSD17B13 reduces enhanced pro-fibrotic inflammaging in NAFLD to retard steatohepatitis and fibrosis.



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2386-C | THE SUN1 H118Y VARIANT ASSOCIATES WITH HISTOLOGIC NAFLD AND INCREASES INSULIN RESISTANCE AND LIPID ACCUMULATION IN HUMAN HEPATOMA CELLS

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Background: Nonalcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease and a growing cause of morbidity and mortality, with no FDA-approved treatment, highly variable progression, and complex environmental and genetic risk factors. We previously reported a genetic link between the common nuclear envelope protein coding variant rs6461378 (g.842031C > T; *SUN1* H118Y) and hepatic steatosis, as well as with NAFLD-related metabolic traits, including insulin resistance. Here we report that *SUN1* H118Y associates with histologic NAFLD and exerts a direct metabolic effect in hepatocyte-like cells *in vitro*. **Methods**: Using publicly available GWAS summary statistics, we performed an association analysis of *SUN1* H118Y with histologic NAFLD in the Elucidating Pathways of Steatohepatitis (EPoS) consortium dataset. A potential direct metabolic impact of SUN1 H118Y was tested in human hepatoma (Huh7 and HepG2) cells using semi-quantitative lipid staining (BODIPY 493/593) and determination of insulin-stimulated AKT phosphorylation via immunoblot, as well as transcriptional analysis (qPCR) of lipid-related gene expression. **Results:** Rs6461378-T positively associated with histologic NAFLD in the EPoS consortium cohort ($P = 0.017$), confirming the prior genetic association results and suggesting a possible direct impact on human liver disease. *In vitro*, HepG2 and Huh7 cells expressing SUN1 H118Y exhibited decreased insulin sensitivity, determined by insulin-stimulated AKT phosphorylation, compared to WT SUN1-expressing cells. Huh7 cells expressing SUN1 H118Y accumulated significantly more lipid than WT SUN1-expressing cells, with or without oleic acid treatment (all $P < 0.01$; Figure 1); a similar effect of SUN1 H118Y on lipid accumulation was seen in HepG2 cells. Further, we conducted a gene expression analysis of lipid regulatory genes to explore the underlying mechanism of lipid accumulation. Huh7 cells expressing SUN1 H118Y showed upregulation of *CD36, ELOVL1*,

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HSC subpopulations and transcriptional programs may play important roles in the transition from advanced fibrosis to cirrhosis in human NASH.
Disclosures: Michael Feigh – Gubra: Employee, Yes, No; Gubra: Stock - publicly traded company (excluding mutual/index funds or pension plans), Yes, No; Gubra: Executive role , Yes, No;
Martin Rønn Madsen – Gubra: Employee, No, No;
The following people have nothing to disclose: Mathias Bonde Møllerhøj, Mikkel P Werge, Mikkel Christensen-Dalsgaard, Sanne Veidal, Lise C.B. Rudkjær, Elisabeth Douglas Galsgaard, Lise Lotte Gluud, Henrik B. Hansen

2410-C | META-ANALYSIS OF RNA-SEQ SIGNATURES ALLOWS FOR ROBUST DECONVOLUTION OF SINGLE CELL LINEAGES IN PATIENTS WITH NASH AND ADVANCED FIBROSIS

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Background: Non-alcoholic Fatty Liver Disease (NAFLD) is a progressive liver disease which can lead to cirrhosis and cancer. Necroinflammation and fibrosis are important intermediary steps prior to developing cirrhosis and they involve alterations in hepatic parenchymal and non-parenchymal cell (NPC) populations. Deconvolution of gene expression can be utilized for molecular phenotyping of cell populations within a tissue and can help better understand the disease pathogenesis and identify therapeutic targets. Aim: To conduct a meta-analysis of multiple human hepatic gene expression datasets for characterizing alterations in cell populations through deconvolution in patients with biopsy-proven NAFLD. **Methods:** We have conducted a meta-analysis of 9 hepatic bulk RNA-Seq and 4 microarray data from patients with human NAFLD. The total number of patients included was 1276; 576 with F0-F1 and 398 with F $\geq$ 3 fibrosis. All data sets are available in the public domain except one. Using the unique top 50 high expression marker genes defined by the log2FC from liver single-cell RNA-seq data and a novel in-house deconvolution algorithm, we characterized 12 individual cell lineages: mononuclear phagocytes (MPs), plasmacytoid DCs, innate lymphoid cells (ILC), T cells, B cells, plasma cells, mast cells, endothelial cells, mesenchyme, mesothelia, hepatocytes, and cholangiocytes. Primary comparison was between advanced hepatic fibrosis ($\geq$F3) vs no/low fibrosis (F0-F1). Single cell deconvolution was conducted by employing the nonparametric Wilcoxon test to calculate the P-value for each dataset and then applied additive method for combining the p-values from the independent datasets. The adjusted meta P-value < 0.05 was considered significant for a cell population difference between two groups. **Results:** Deconvolution was initially conducted on individual bulk RNA-Seq and microarray datasets based on differentially expressed genes between F $\geq$ 3 and F1-F0 and a meta-analysis of 13 deconvolution datasets was subsequently undertaken. Table 1 summarized cell lineages that are significantly different between F $\geq$ 3 and F0-F1 groups. Among those cell types, F $\geq$ 3 patients have increased cell proportions of several NPCs, including pDC, T cells, B cells, plasma cells, mast cells, endothelia, mesenchyme, and cholangiocytes when compared to F0-F1. **Conclusion:** Transcriptomic meta-analysis combined with deconvolution has identified a number of non-parenchymal cell lineages which are increased in the livers of patients with NASH and advanced fibrosis, highlighting the complexity of NASH pathobiology and the importance of targeting NPC cross-talk when exploring new therapeutic strategies.

Cell types	Cell propotion F≥3 higher than F0-F1	Cell propotion F≥3 less than F0-F1
MPs	0.6743	1
pDCs	**0.0026**	1
ILCs	0.0705	1
T cells	**0.0000**	1
B cells	**0.0003**	1
Plasma B cells	**0.0019**	1
Mast cells	**0.0001**	1
Endothelia	**0.0000**	1
Mesenchyme	**0.0001**	1
Mesothelia	0.0864	1
Hepatocytes	0.9786	0.298419962
Cholangiocytes	**0.0000**	1

Table 1. Differences in single cell lineages in the liver of NASH with advanced fibrosis from the meta-analysis of 13 datasets. Bolded adjusted meta-P value indicates significant difference between groups ($p<0.05$). Abbreviations: MPs: Mononuclear phagocytes; pDCs: Plasmacytoid dendritic cells; ILCs: Innate lymphoid cells.

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Disclosure information not available at the time of publication: Sha Cao, Tiebing Liang

♦ 2412-C | NOVEL DIGITAL PATHOLOGY QUANTITATIVE IMAGE ANALYSIS AND AI METHOD DETECTS TRAITS OF FIBROSIS TREATMENT RESPONSE.

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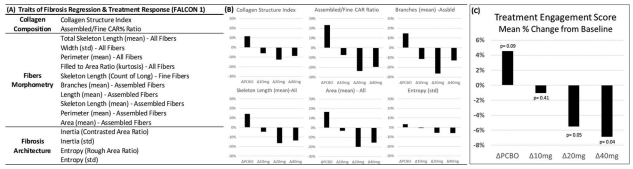
Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA

Background: Manual histological evaluation of liver biopsy is the gold standard method for fibrosis staging in Non-Alcoholic Steatohepatitis (NASH), but it is limited by its inter and intra-reader variability. The use of single-fiber, quantitative and high resolution Digital Pathology image analysis offers the to describe specific traits that account for disease progression and/or regression or treatment response. In this exploratory post-hoc analysis, we used FibroNest digital pathology to identify fibrosis traits of treatment, and dose response from the phase 2b FALCON1 study of pegbelfermin (PGBF) in NASH (NCT0348699). **Methods:** Eligible adults were 18-75 years of age (N = 197) with NASH and stage 3 fibrosis diagnosed by histologic assessment of liver biopsy according to NASH CRN criteria. During the 48-week double-blind treatment period, patients received subcutaneous 10mg, 20mg, or 40mg PGBF or placebo once weekly. Liver biopsies were obtained up to six months prior to or during screening and at week 24. Formalin-fixed, paraffin embedded sections of the liver biopsies were stained with Masson Trichrome and imaged at 40X. Each digital image was evaluated for quality along 20 dimensions (tissue processing, staining, and scanning) to generate a Digital Biopsy Adequacy Score (DBA). Quantitative image analysis was performed to extract single-fiber quantitative traits (qFTs, N = 315) from the fibrosis composition, morphometric and architectural histological phenotypes. Traits that exhibited a significant ($p < 0.05$) and meaningful ($> 20\%$) mean change from baseline were identified and reported, and then normalized and combined in a composite score of Treatment Engagement (TrES). **Results:** Groups sizes ranged from 34 to 39 per group for patients with paired data following removal of those samples considered nonvaluable for Pharmanest algorithms (i.e., DBA < 5). We identified 26 traits of response, 16 of which were readily interpretable (Fig. A, B). P-values of the group mean % change from baseline of the TrES for the placebo, 10mg, 20mg, 40mg groups are 0.09, 0.41, 0.05 and 0.04 respectively. The TrES relative % change from baseline exhibits a dose response trend (Fig), consistent with previous published results with some biomarkers (doi.org/10.1016/j.jhepr.2022.100661). The TrES corresponds well with NASH-CRN Fibrosis stages, but with a performance that is less than the FibroNest Phenotypic Fibrosis Score (Ph-FCS, as reported previously) at low levels of fibrosis (F1-2). **Conclusion:** Twenty-six histological traits of treatment response are identified with high-resolution digital Pathology methods and evaluated in the context of the PGBF intervention. The related Treatment Engagement composite continuous score detects the antifibrotic effect of PGBF treatment with moderate performance as seen for similar outcomes (Histology, fibrotic biomarkers) reported for this study.



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Arun Sanyal – Durect: Stock – privately held company (individual stocks and stock options), No, No; GenFit: Stock – privately held company (individual stocks and stock options), No, No; Gilead: Consultant, No, No; Novartis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genetech: Consultant, No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Path-AI: Consultant, No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Histoindex: Consultant, No, No; Fibronest: Consultant, No, No; Hemoshear: Stock – privately held company (individual stocks and stock options), No, No; Hemoshear: Consultant, No, No; Inversago: Stock – privately held company (individual stocks and stock options), No, No; Biocellvia: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Eli Lilly: Consultant, No, No; Novo Nordisk: Consultant, No, No; Boehringer Ingelheim: Consultant, No, No; Astra Zeneca: Consultant, No, No; Boehringer Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Akero: Consultant, No, No; Intercept:

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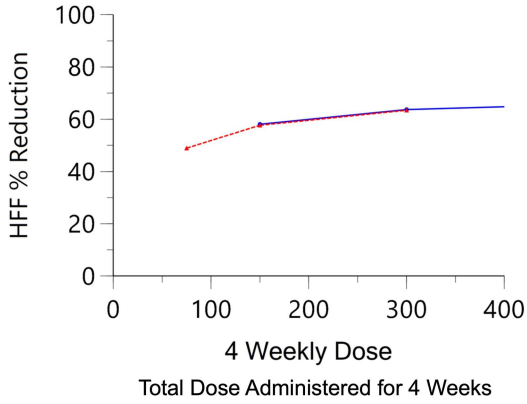
The following people have nothing to disclose: Zachary D. Goodman

2413-C | POPULATION PHARMACOKINETIC/PHARMACODYNAMIC MODELING OF HEPATIC FAT FRACTION SUGGESTS EQUIVALENT EFFICACY BETWEEN ONCE MONTHLY AND BI-WEEKLY DOSING OF BOS-580 IN PHENOTYPIC NASH PATIENTS

Swapan Chowdhury[1], Aruna Dontabhaktuni[2], Tatjana Odrljin[1], Alicia Clawson[1], Etienne Dumont[1], Vijay Bhargava[3], Eric Svensson[1] and Serge Guzy[4], (1)Boston Pharmaceuticals, (2)Pharmapro Consulting Inc., (3) Nejay Consultant Inc, (4)Poppharm

Background: FGF-21 analogs have been shown to increase NASH resolution and improve fibrosis in NASH patients with once weekly and bi-weekly dosing. BOS-580 is an investigational FGF21-IgG fusion protein engineered to have an extended serum half-life in humans. In a healthy volunteer Phase 1 study, BOS-580 showed a dose-dependent increase in exposure with a terminal half-life of approximately 21 days following subcutaneous administration, suggesting the feasibility of bi-weekly or once monthly dosing. **Methods:** A Phase 2a study was designed to examine the safety, pharmacokinetics, and pharmacodynamics of a range of dose levels and dosing frequencies in a 12-week treatment period to identify an optimal regimen for patients with phenotypic NASH. Pharmacodynamic endpoints included % change from baseline in hepatic fat fraction as measured by MRI-PDFF. This study enrolled 102 patients, with a VCTE LSM score of 7-9.9 kPa, AST > 20 IU/ml, and MRI-PDFF ≥ 10%. BOS-580 PK data from phase 1 studies with rich PK sampling were used to generate population PK (Pop-PK) estimates for BOS-580 that were then used to perform Bayesian analysis on the Phase 2a PK data with sparse sampling. A sequential PK/PD analysis followed on the MRI-PDFF data and individual predicted PK profiles from the Bayesian analysis. The PK/PD model was an indirect response model with MRI-PDFF reduction by the predicted drug concentration. A simultaneous PK/PD fit was performed to assess % change from baseline in MRI-PDFF for different doses and dosing regimens, and to determine the dose/regimen required to achieve 30, 50, and 70% MRI-PDFF reduction. **Results:** Pop-PK analysis identified dose proportional increases in AUC_{tau} at steady state; exposure was independent of dosing regimen for same total monthly dose. There was a good fit, with no obvious bias in the observed vs predicted PK and MRI-PDFF data. The PK/PD model predicted with high confidence the following: a) median % MRI-PDFF reduction with 150mg to 300mg monthly dose ranged from ~57-62% (Figure 1), b) at doses ≥ 200mg monthly, > 70% of patients are predicted to reduce MRI-PDFF by > 50%, and c) the % reduction in MRI-PDFF is similar whether a total monthly dose is given bi-weekly or once-a-month (Figure 1). **Conclusion:** Once monthly dosing of BOS-580 appears to be as effective as bi-weekly dosing for the reduction of liver fat in patients with phenotypic NASH, supporting the notion that BOS-580 is an FGF-21 analog capable of once monthly dosing.

Figure 1: Median Model Predicted % HFF Reduction at Week 12 as a Function of Total Dose Administered for Both ---- Q4W and ---- Q2W



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induced obesity (DIO) mouse model where male C57BL/6J mice were fed with a high fat diet for 14 weeks, followed by once daily (QD) or twice daily (BID) oral administration of ALG-055009 for 28 days. Pharmacodynamic endpoints included total/LDL cholesterol, liver enzymes, and thyroid hormones. Liver and heart gene expression was determined by qPCR. Repeat-dose toxicology studies were conducted in rats and dogs, up to 13-weeks in duration, and clinical pathology endpoints including thyroid hormones were assessed at 2-, 6-, and 13-weeks, as well as following 2- to 4-weeks of recovery. **Results:** In the DIO mouse model, where ALG-055009 was administered QD or BID for 28 days, dose-dependent increases in selective THRβ-induced liver gene expression were observed and were associated with reductions in serum total and LDL-C. In this model, 0.15 mg/kg BID was defined as the minimal efficacious dose, corresponding to ALG-055009 plasma C_{max} of 82.5 ng/mL, AUC_{0-24} of 515 ng•h/mL and C_{min} of 2.01 ng/mL. ALG-055009 is projected to have low potential for drug-drug interactions in humans, either as a perpetrator or victim. Additionally, ALG-055009 was well tolerated in both rats and dogs in repeat dose toxicology studies up to the highest doses tested. Dose-dependent changes in lipid parameters were observed in repeat-dose toxicology studies, whereas changes in total circulating thyroid hormones levels were observed at supratherapeutic exposures. **Conclusion:** ALG-055009 is a potent and selective THR-β agonist with favorable in vitro safety and ADME properties and repeat-dose toxicity profile in rats and dogs. ALG-055009 also dose-dependently reduced levels of atherogenic lipids. Combined, this profile indicates ALG-055009 has the potential to be a best-in-class THR-β agonist for the treatment of NASH.

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2462-C | RESMETIROM IMPROVES THE ATHEROGENIC LIPID/LIPOPROTEIN PROFILE IN PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS: 52-WEEK DATA FROM THE PHASE 3 MAESTRO-NASH TRIAL

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Background: Cardiovascular disease (CVD) is a common cause of mortality in patients with nonalcoholic steatohepatitis (NASH). Data from the Phase 3 MAESTRO-NAFLD-1 trial demonstrated that resmetirom, an oral liver-targeted thyroid hormone receptor-β selective agonist, significantly improves the atherogenic lipid/lipoprotein profile in patients with presumed NASH. MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy-confirmed NASH and fibrosis. Here we report data from MAESTRO-NASH demonstrating the effect of resmetirom on atherogenic lipid and lipoprotein levels. **Methods:** Adults with ≥3 metabolic risk factors, liver stiffness ≥8.5 kPa, hepatic fat ≥8%, biopsy-confirmed NASH with F1B-F3 fibrosis, and a nonalcoholic fatty liver disease activity score (NAS) ≥4 were eligible to participate in MAESTRO-NASH. Patients were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo administered once daily. Dual primary endpoints at Week 52 were achievement of NASH resolution with no worsening of fibrosis or ≥1-stage improvement in fibrosis with no worsening of NAS. The key secondary endpoint was percent change from baseline in low-density lipoprotein cholesterol (LDL-C) at Week 24. Additional endpoints included percent change from baseline in triglycerides, apolipoprotein B (apoB), apolipoprotein CIII (apoCIII), and lipoprotein (a) (Lp(a)). **Results:** As reported previously, both primary endpoints were achieved with both resmetirom 80 and 100 mg ($p < 0.0002$ vs placebo for all). At Week 24, LDL-C levels were significantly reduced from baseline with resmetirom 80 and 100 mg compared with placebo ($p < 0.0001$ vs placebo for both) (TABLE). In addition, triglycerides, apoB, apoCIII, and Lp(a) were significantly reduced from baseline with resmetirom versus placebo treatment at Week 24 ($p < 0.0001$ vs placebo for all); the significant reductions achieved with resmetirom treatment were maintained at Week 52. **Conclusion:** Resmetirom 80 and 100 mg significantly reduced atherogenic lipid/lipoprotein levels from baseline, including triglycerides, apoB, apoCIII, and Lp(a), by Week 24. Furthermore, improvements in the lipid/lipoprotein profile were

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maintained over 52 weeks. The effect of potential NASH therapies on cardiovascular risk factors, including atherogenic lipids/lipoproteins, is important to consider as CVD is a common cause of mortality in patients with NASH and fibrosis.

TABLE. Percent change from baseline in lipid/lipoprotein levels at Weeks 24 and 52.

	RES 80 mg	RES 100 mg	PBO	Treatment Difference RES 80 mg vs PBO (95% CI) p-value	Treatment Difference RES 100 mg vs PBO (95% CI) p-value
LDL-C (mg/dL)					
Baseline mean (SD)	106.6 (37.8)	102.9 (37.6)	106.2 (41.4)		
Week 24 LSM %CFB (SE)	-13.6 (1.7)	-16.3 (1.7)	0.1 (1.7)	-13.7 (-17.5, -10.0) <0.0001	-16.4 (-20.1, -12.6) <0.0001
Baseline mean (SD)	106.9 (37.9)	102.9 (36.8)	106.1 (41.7)		
Week 52 LSM %CFB (SE)	-13.7 (1.8)	-19.5 (1.9)	-0.4 (1.7)	-13.3 (-17.3, -9.3) <0.0001	-19.0 (-23.0, -15.1) <0.0001
Triglycerides (mg/dL) Among patients with baseline triglycerides >150 mg/dL					
Baseline mean (SD)	237.9 (120.7)	244.7 (132.8)	261.5 (146.0)		
Week 24 LSM %CFB (SE)	-22.7 (4.0)	-21.7 (4.3)	-2.6 (4.1)	-20.1 (-28.3, -11.8) <0.0001	-19.1 (-27.8, -10.3) <0.0001
Baseline mean (SD)	241.0 (122.4)	252.1 (160.2)	256.5 (145.7)		
Week 52 LSM %CFB (SE)	-22.5 (4.2)	-28.4 (4.5)	-3.5 (4.2)	-19.0 (-27.9, -10.1) <0.0001	-24.9 (-34.1, -15.7) <0.0001
ApoB (U/L)					
Baseline mean (SD)	98.4 (28.1)	95.9 (28.3)	97.5 (32.1)		
Week 24 LSM %CFB (SE)	-16.8 (1.3)	-19.8 (1.3)	0.4 (1.3)	-17.2 (-20.0, -14.4) <0.0001	-20.2 (-22.9, -17.4) <0.0001
Baseline mean (SD)	98.5 (27.6)	95.6 (27.8)	97.1 (32.1)		
Week 52 LSM %CFB (SE)	-16.2 (1.5)	-22.3 (1.5)	0.6 (1.4)	-16.8 (-20.0, -13.7) <0.0001	-22.9 (-26.0, -19.7) <0.0001
ApoCIII (mg/dL)					
Baseline mean (SD)	10.9 (4.7)	10.7 (5.3)	10.5 (5.6)		
Week 24 LSM %CFB (SE)	-10.6 (3.6)	-14.1 (3.1)	8.1 (3.1)	-18.7 (-27.1, -10.4) <0.0001	-22.2 (-29.0, -15.4) <0.0001
Baseline mean (SD)	10.9 (4.7)	10.7 (5.5)	10.3 (5.5)		
Week 52 LSM %CFB (SE)	-10.0 (3.8)	-17.1 (3.3)	9.8 (3.3)	-19.8 (-28.4, -11.1) <0.0001	-26.9 (-34.1, -19.6) <0.0001
Lp(a) (nmol/L) Among patients with baseline Lp(a) >10 nmol/L					
Baseline mean (SD)	62.0 (67.5)	58.7 (64.6)	57.9 (70.2)		
Week 24 LSM %CFB (SE)	-30.4 (3.8)	-35.9 (4.0)	-0.8 (3.5)	-29.5 (-37.6, -21.5) <0.0001	-35.1 (-43.5, -26.6) <0.0001
Baseline mean (SD)	64.5 (68.4)	57.6 (62.7)	57.7 (70.0)		
Week 52 LSM %CFB (SE)	-34.5 (5.0)	-37.5 (5.7)	-5.0 (4.6)	-29.5 (-39.4, -19.6) <0.0001	-32.4 (-43.1, -21.8) <0.0001

ApoB, apolipoprotein B; ApoCIII, apolipoprotein CIII; CFB, change from baseline; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); LSM, least squares mean; PBO, placebo; RES, resmetirom; SD, standard deviation; SE, standard error.

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♦ 2463-C | RESMETIROM TREATMENT HELPS RESTORE THYROID HORMONE LEVELS IN PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS: 52-WEEK DATA FROM THE PHASE 3 MAESTRO-NASH TRIAL

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Background: Thyroid hormone receptor (THR)-β regulates various metabolic pathways within the liver. However, patients with nonalcoholic steatohepatitis (NASH) have diminished hepatic THR-β signaling (due to decreased conversion of prohormone T4 to active hormone T3 in favor of increased conversion of T4 to inactive metabolite reverse T3 [rT3]). Resmetirom, an oral

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liver-targeted THR-β selective agonist in development as a potential treatment for NASH, may address this underlying pathophysiology. Here we report data from the Phase 3 MAESTRO-NASH trial on the effect of 52 weeks of resmetirom treatment on thyroid hormone levels. **Methods:** MAESTRO-NASH (NCT03900429) is an ongoing randomized, double-blind, placebo-controlled trial to evaluate the efficacy of resmetirom in adults with biopsy-confirmed NASH and fibrosis. Eligible patients were adults with ≥3 metabolic risk factors, liver stiffness ≥8.5 kPa, hepatic fat ≥8%, biopsy-confirmed NASH with F1B-F3 fibrosis, and a nonalcoholic fatty liver disease activity score ≥4. Patients were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo administered once daily. Circulating thyroid hormone levels (thyroid-stimulating hormone [TSH], free T3 [FT3], free T4 [FT4], and rT3) as well as the FT3/rT3 ratio were evaluated at Week 52 in the overall population, thyroxine-treated population, and euthyroid population. **Results:** In the overall population at Week 52, no significant change from baseline was observed in TSH or FT3 levels in either the 80- or 100-mg resmetirom group compared with placebo (TABLE). However, FT4 and rT3 levels were significantly reduced from baseline at Week 52 in both resmetirom groups compared with placebo ($p < 0.0001$ vs placebo for all). At Week 52, the FT3/rT3 ratio was also significantly increased with resmetirom versus placebo treatment ($p < 0.0001$ vs placebo for both resmetirom doses). Similar effects as reported for the overall population were noted in the thyroxine-treated and euthyroid populations. **Conclusion:** Resmetirom treatment did not reduce TSH or FT3 levels consistent with no impact on the central thyroid axis. In contrast, resmetirom treatment significantly reduced FT4 and rT3 levels consistent with increased conversion of T4 to active hormone T3 and decreased conversion of T4 to the inactive metabolite rT3. Overall, these data suggest resmetirom treatment may restore thyroid hormone levels within the liver of patients with NASH and fibrosis.

TABLE. Change from baseline in thyroid hormone levels at Week 52 in the overall population from MAESTRO-NASH.

	RES 80 mg	RES 100 mg	Placebo	Treatment Difference RES 80 mg vs Placebo (95% CI) p-value	Treatment Difference RES 100 mg vs Placebo (95% CI) p-value
TSH (mIU/L)					
Baseline mean (SD)	2.0 (1.14)	2.1 (1.17)	2.0 (1.14)		
Week 52 CFB (SE)	-0.3 (0.06)	-0.2 (0.06)	-0.1 (0.06)	-0.2 (-0.3, -0.1) 0.0057	-0.1 (-0.3, 0) 0.1290
FT3 (ng/L)					
Baseline mean (SD)	3.0 (0.41)	3.0 (0.48)	3.0 (0.41)		
Week 52 CFB (SE)	0 (0.03)	-0.1 (0.03)	0 (0.03)	0 (-0.1, 0.1) 0.6058	-0.1 (-0.1, 0) 0.1282
FT4 (ng/dL)					
Baseline mean (SD)	1.1 (0.19)	1.1 (0.21)	1.1 (0.17)		
Week 52 %CFB (SE)	-13.9 (0.96)	-18.1 (0.97)	2.6 (0.92)	-16.6 (-18.6, -14.5) <0.0001	-20.7 (-22.8, -18.6) <0.0001
Week 52 CFB (SE)	-0.2 (0.01)	-0.2 (0.01)	0 (0.01)	-0.2 (-0.21, -0.16) <0.0001	-0.2 (-0.3, -0.2) <0.0001
rT3 (ng/dL)					
Baseline mean (SD)	18.5 (5.41)	19.2 (6.17)	18.4 (5.60)		
Week 52 CFB (SE)	-4.6 (0.31)	-5.1 (0.32)	0.2 (0.30)	-4.7 (-5.4, -4.1) <0.0001	-5.2 (-5.9, -4.6) <0.0001
FT3/rT3					
Baseline mean (SD)	0.270 (0.0886)	0.263 (0.0824)	0.276 (0.0895)		
Week 52 CFB (SE)	0.09 (0.007)	0.10 (0.007)	-0.01 (0.006)	0.10 (0.08, 0.11) <0.0001	0.10 (0.09, 0.12) <0.0001

CFB, change from baseline; CI, confidence interval; FT3, free T3; FT4, free T4; RES, resmetirom; rT3, reverse T3; SD, standard deviation; SE, standard error; TSH, thyroid-stimulating hormone.

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2464-C | SEMAGLUTIDE AND LANIFIBRANOR DIFFERENTIALLY ALTER NASH AND LIVER FIBROSIS IN DIET-INDUCED OBESE HAMSTERS WITH OR WITHOUT FREE ACCESS TO ALCOHOL

Francois Briand, Natalia Breyner, Estelle Grasset and Thierry Sulpice, Physiogenex

Background: GLP-1 receptor agonist semaglutide (SEMA) and pan-PPAR agonist lanifibranor (LANI) are currently evaluated in humans for NASH treatment. While chronic alcohol intake may aggravate liver lesions in patients, rodent studies suggested that both GLP-1 and PPAR agonists reduce alcohol intake in mouse and rat, but these species are not truly alcohol dependent. The golden Syrian hamster spontaneously shows a high preference for alcohol and may represent a better animal model. Here we tested the effects of SEMA and LANI in diet-induced obese hamsters, a preclinical model with human-like NASH, with or without free access to alcohol. **Methods:** Hamsters' preference for alcohol and selection of alcohol % in drinking water were first confirmed in pilot studies. Next, obesity and NASH were induced with a free choice diet, which

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holistic approach for treating NASH accompanied by fibrosis. To address this complex condition, we developed a novel tetra-specific drug called OGB21502 by combining GLP-1, GCG, FGF21 and IL-1RA using UniStac platform. In this study, we evaluate the effect of OGB21502 in GAN (Gubra-Amylin NASH) diet-induced obese (DIO) and CCl_4-induced mouse model. **Methods:** To induce obese mice, Male C57BL/6 mice were divided into two groups and subjected to a normal diet or a GAN diet, high in saturated fat (40%), fructose (22%), and cholesterol (2%) for 30 weeks. In the remaining 8 weeks, the mice were administered either OGB21502 or reference drugs (Fc-FGF21, obeticholic acid and semaglutide). In the second study, CCl_4-liver fibrosis model was induced by intraperitoneal injections (I.P.) of CCl_4 for 6 weeks. The OGB21502 or comparative control, obeticholic acid was subcutaneously administered for the last 4 weeks. After treatment, liver tissue and blood samples were used to evaluate histopathological characteristics and markers associated with steatosis and fibrosis. **Results:** In GAN-DIO mice, OGB21502 treatment resulted in reduction in liver weight, ALT and cholesterol levels compared to reference drugs. Notably, OGB21502 led to an improvement in levels of fasting blood glucose and insulin. In the CCl_4-induced mice model, treatment with the tetra-specific drug, OGB21502, demonstrated improved effects in liver inflammation and fibrosis score compared to dual (GLP-1/GCG) or triple (GLP-1/GCG/FGF21) treatments. OGB21502 reduced liver injury markers, including blood ALT and total bilirubin levels. Furthermore, the expression levels of fibrotic markers such as TGF-β, α-SMA, and LOLX-2 were significantly decreased in the OGB21502 treatment group. **Conclusion:** Overall, a novel tetra-specific drug, OGB21502 improved glucose level, insulin resistance, liver damage, inflammation as well as liver fibrosis through multiple animal models. These results demonstrate the potential of OGB21502 as an important alternative for treating severe NASH with metabolic dysfunction and fibrosis, due to synergistic effects across multiple targets.

Disclosures: The following people have nothing to disclose: Ji-Hye Kim, Yunki Kim, Junyeob Lee, Jeonghwa Lee, Nakho Chang, DaeSeong Im, Sungjin Park

2472-C | THERAPEUTIC HUMAN PLASMA FRACTION REVERSES HIGH FAT DIET-INDUCED LIVER TRANSCRIPTOME AND IMPROVES LIVER REGENERATION

Benson Lu, Alkahest

Background: The robust regenerative capacity of the mammalian liver declines with age and presence of steatosis. Heterochronic parabiosis between young and old mice demonstrated that exposure of aged liver to young circulation restores hepatocyte proliferation, suggesting that liver regeneration can be enhanced by altering the plasma proteome. However, the circulating factors responsible for driving the mechanisms of rejuvenation in aged hepatocytes have not been defined. In addition, it is unknown if the effect can be recapitulated by administration of human plasma proteins with the potential for therapeutic translation. We utilized a manufacturing scale subfraction approach to identify a therapeutically relevant human plasma fraction (PF) that enhances liver regenerative potential in a mouse model of partial hepatectomy. **Methods:** 20 month old C57/B6 mice were fed with high fat diet (HFD) or normal chow for 6 weeks before i.v. injection of PF or recombinant Secreted Phosphoprotein 1 (SPP1). 70% partial hepatectomy was performed post treatment and liver regeneration was evaluated with proliferation index. Single-nuclei RNA-seq was performed to compare liver transcriptome with HFD and PF treatment. **Results:** We found that PF increased liver regeneration and decreased senescence post hepatectomy in aged mice with steatosis. We further employed single-nuclei RNA-seq to interrogate transcriptomic landscape mediated by PF. We found that signatures altered by HFD were reversed by PF, specifically in pathways involving metabolism of lipids, amino acids, and bile acids. PF proteomic analysis, combined with liver RNA-seq, SPP1 as a candidate bioactive within PF that contributes to its activity in liver regeneration. Administration of recombinant SPP1 increased hepatocyte proliferation post hepatectomy. Utilizing a SPP1-derrived peptide with a restricted integrin receptor binding profile, we further defined a SPP1-driven mechanism critical for liver regeneration. **Conclusion:** Together, our data provide a therapeutically relevant approach to reverse age-related and HFD-induced decline of liver regeneration by altering the plasma proteomic composition. SPP1 is one of the several bioactive components identified within PF, demonstrating that our PF proteomic dataset will enable discovery and confirmation of additional drivers of activity to provide a deep mechanistic understanding for therapeutic modulation of liver regeneration.

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♦ 2473-C | TOPLINE RESULTS FROM THE REVERSE TRIAL OF OBETICHOLIC ACID IN PATIENTS WITH COMPENSATED CIRRHOSIS DUE TO NONALCOHOLIC STEATOHEPATITIS

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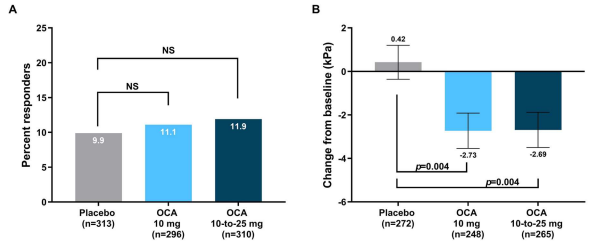
Background: Obeticholic acid (OCA) is a first-in-class farnesoid X receptor agonist and antifibrotic agent in development for treatment of liver fibrosis due to nonalcoholic steatohepatitis (NASH). This phase 3 randomized, double-blind, placebo-controlled multicenter study evaluated the efficacy and safety of OCA in patients with compensated cirrhosis due to NASH. **Methods:** Patients with biopsy-confirmed compensated cirrhosis and no esophageal varices were randomized 1:1:1 to receive once-daily oral placebo, OCA 10 mg, or OCA 10-to-25 mg (OCA 10 mg titrated to 25 mg at month 3 if no safety or tolerability concerns). The primary endpoint was histological improvement in fibrosis by $\geq$1 stage with no worsening of NASH at month 12-18 by consensus read. Safety was assessed by treatment-emergent adverse events (TEAEs) and adjudicated cardiovascular, hepatic, and renal safety events. **Results:** The intent-to-treat population (N = 919) was mostly White (87%) and female (66%) with an average age of 60 years and diabetes at baseline (78%). Improvement of fibrosis by $\geq$1 stage without worsening of NASH occurred in 9.9% (placebo), 11.1% (OCA 10 mg), and 11.9% (OCA 10-to-25 mg) (Figure 1A). Reductions in liver stiffness by transient elastography occurred with OCA compared with placebo (Figure 1B). OCA resulted in reduced ALT levels vs placebo. TEAEs, serious TEAEs, and deaths were balanced across treatment groups. Pruritus was the most common TEAE. There were no fatal, irreversible, or severe adjudicated hepatic safety events related to OCA. Three events were adjudicated as moderate and possibly related to OCA; 2 (peak total bilirubin [TB] 3.5, 4.1 mg/dL) resolved with discontinuation of OCA; the third patient (peak TB 4.2 mg/dL) continued to experience fluctuations in laboratory values after discontinuing OCA. Serious gallbladder-related events occurred in $\leq$1% of subjects in all treatment groups. No difference was observed in adjudicated major cardiovascular events and acute kidney injury events across treatment groups. **Conclusion:** Histological reversal of cirrhosis over a short period is challenging. Although REVERSE did not meet its primary histological endpoint, reductions in liver stiffness with OCA suggest disease improvement. Other noninvasive tests and a more granular assessment of collagen burden may provide further insight into OCA's impact on cirrhosis. Notably, no deaths, liver transplants, or irreversible liver injury events related to OCA were observed in patients with compensated cirrhosis.

Figure 1. Efficacy of OCA in Patients with Compensated Cirrhosis. Improvement of fibrosis by ≥1 stage without worsening of NASH at month 12-18 **(A)** and change from baseline to month 18 in liver stiffness measurement by transient elastography **(B)**.



(A) "No worsening of NASH" was defined as no worsening of hepatocellular ballooning grade, of lobular inflammation grade, or of steatosis grade. (B) Data are least squares mean ± SE calculated using mixed effect repeated measure model with treatment group, visit, visit by treatment interaction, and stratification factors (type 2 diabetes at enrollment) as fixed effects, and baseline as a covariate. Mean (±SD) baseline liver stiffness (kPa) was 22.11 (12.18), 22.85 (12.53), and 23.13 (12.30) for placebo, OCA 10 mg, and OCA 10-to-25 mg, respectively.

Abbreviations: kPa, kilopascal; NASH, nonalcoholic steatohepatitis; NS, not statistically significant; OCA, obeticholic acid.

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Arrowhead Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; AstraZeneca: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Boehringer-Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bristol-Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Eli Lilly: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; 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2474-C | TYROSOL REDUCES NASH-ASSOCIATED STEATOSIS, FIBROSIS AND INFLAMMATION BY MODULATING THE HEPATIC IMMUNE PHENOTYPE: PRECLINICAL EVIDENCES

Daniela Gabbia, Katia Sayaf, Martina Colognesi, Ilaria Zanotto, Francesco Paolo Paolo Russo and Sara De Martin, University of Padova

Background: The management of NAFLD and NASH represents a clinical challenge. Beneficial effects on liver health have been demonstrated by tyrosol (Tyr), a phenolic compound extracted from extra virgin olive oil. This study aims at evaluating Tyr effects on the hepatic and extrahepatic manifestations of metabolic liver diseases by using experimental 2D and 3D *in vitro* cellular models and a mouse model of NASH. **Methods:** The effect of Tyr *in vitro* was evaluated in 1) HepG2 cells treated with a palmitic:oleic acid mixture to induce fatty acid (FA) accumulation (fatty HepG2), 2) a co-culture of THP1-derived M1 macrophages and fatty HepG2, 3) multicellular spheroids of fatty HepG2, LX2 and THP1-derived macrophages mimicking the inflammatory NASH microenvironment. NASH was induced to C57BL6 mice with a high fructose-high fat diet administered for 14 weeks, combined to CCl_4 treatment (IP 0.05 ml/kg) in the last 4 weeks ($n = 12$). Tyr (10 mg/kg) was administered daily by oral gavage from week 4 ($n = 6$). A group of mice fed with standard diet ($n = 6$) was used as control. The open field, grid and rotarod tests were performed to evaluate NASH-related CNS disorders and sarcopenia. Liver histology was performed by H&E, Masson's trichrome, and ORO stainings. The protein expression of profibrotic αSMA and pro-oxidant NADPH oxidase isoform NOX1 was evaluated by IHC. Hepatic infiltration of CD4+, CD8+ lymphocytes, Tregs, M1- and M2- macrophages was assessed by means of FACS. **Results:** Tyr reduced FA accumulation in HepG2 cells in all the in vitro models ($p < 0.05$. In vivo, Tyr reduced steatosis, fibrosis, and the increase of aSMA expression observed in NASH animals ($p < 0.01$), as well as the number of hepatic inflammatory foci ($p < 0.05$). Tyr reduced NOX1 expression ($p < 0.05$). A drop of proinflammatory CD45+ F4/80+ CD86+ M1-type macrophages ($p < 0.05$), CD4+ ($p < 0.05$) and T helper effector CD4+ FoxP3- CD62L-lymphocytes ($p < 0.05$), and a concomitant increase of Treg CD4+ FoxP3+ cells ($p < 0.05$) was induced by Tyr. Moreover, Tyr attenuated fatigue and anxious behavior in NASH mice, restoring behevioral performances similar to those of healthy animals. **Conclusion:** In preclinical models, Tyr is effective in reducing steatosis, fibrosis, oxidative stress and inflammation, helping the resolution of NASH.
Disclosures: The following people have nothing to disclose: Daniela Gabbia, Katia Sayaf, Martina Colognesi, Ilaria Zanotto, Francesco Paolo Paolo Russo, Sara De Martin

2475-C | A NATIONAL SURVEY ON THE RISING ROLE OF ENDOSCOPIC BARIATRIC PROCEDURES FOR THE MANAGEMENT OF NONALCOHOLIC STEATOHEPATITIS

Diana Jomaa[1], Yervant Ichkhanian[1], Yara Dababneh[1], Patrick Brown[1], Duyen Dang[1], Humberto Gonzalez[2], Deepak Venkat[1] and Tobias Zuchelli[1], (1)Henry Ford Hospital, (2)Henry Ford Health

Background: Weigh loss is the cornerstone of halting disease progression in patients with non-alcoholic fatty liver disease (NAFLD) and preventing nonalcoholic steatohepatitis (NASH). Patients who fail

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to lose weight through conservative modalities are often offered the option of bariatric surgeries, but most patients are either high-risk surgical candidates or prefer non-surgical modalities. Endoscopic Sleeve Gastrectomy (ESG) was introduced as a minimally invasive bariatric procedure that provides patients with acceptable weight loss and improvement in their metabolic disease that contributes to NAFLD and NASH. In the study, we aimed to conduct a national survey to evaluate practicing gastroenterologist's perception on the role of ESG for managing NASH. **Methods:** We conducted a descriptive study through a national survey of 15 questions. The survey was built through an online cloud-based software, and a link was emailed to a total of 493 U.S. GI fellowship programs. The email recipients were asked to forward the survey link to additional faculty members. There was no monetary compensation for filling out the survey. The survey was anonymous, and no physician or patient identifier was shared. Total estimated time for completing the survey was 4 minutes. **Results:** A total of 54 responses were obtained during the time period 01-09-2021 and 2-12-2021, with estimated completion rate of 50%. Survey questions were summarized in Table 1. The majority of participants, 72%, were from tertiary care academic center, mostly commonly located in the Midwest, (39%). About half (48%) of the institutions had an established multi-disciplinary team to manage patients with NASH who failed to lose weight following conservative modalities, with 65% having an advanced endoscopist trained in bariatric endoscopy in the team. Providers were most commonly, advanced endoscopists (40%), hepatologists (26%), general gastroenterologists, (18%), and gastroenterology fellows (11%). More than half of the participants (62%) encountered NASH patients "sometimes" with BMI > 40 kg/m2 who failed the current standard of care noninvasive weight loss measures, and refused surgical bariatric procedures, or deemed not to be a surgical candidate. Providers reported that endoscopic bariatric options, most commonly ESG (80%), are "sometimes" discussed with the patients in 46% of the times. Barriers for referral for endoscopic bariatric procedures in NASH patients were overwhelmingly due to lack of insurance coverage in 86% of the times while 32% of the participants thought that there was still not enough literature. Advanced endoscopists reported that they are unable to obtain insurance coverage for managing NASH patients in 78% of the time. **Conclusion:** NASH is projected to be the leading cause of cirrhosis, and the utilization of novel management modalities such as ESG are overwhelmingly impacted by the health insurance reimbursement policies.

Table 1. Survey Questions

Questions	Choices
Which best identifies you?	General Gastroenterologist, Hepatologist, Advanced Endoscopist, Motility Specialist, IBD Specialist, GI fellow, Advanced Endoscopy fellow, IBD fellow, Motility fellow, Hepatology fellow
How would you describe the hospital/health system you work at?	Tertiary care academic center, Veteran's system, Community hospital, Private group practice
What region of the country do you practice in?	Northeast, Southeast, Midwest, West
If you are currently involved in scholarly activity, insert your H-index	"free text"
Do you have an established multidisciplinary team to discuss NASH patients who fail noninvasive weight loss measures, including pharmacotherapy, to achieve a sustainable total body weight loss (TBWL) of at least 5%?	Yes, No
Do you have an advanced endoscopist trained in bariatric procedures in your multidisciplinary NASH team?	Yes, No
How often do you encounter NASH patients with BMI>40 kg/m2 who failed the current standard of care noninvasive weight loss measures, including pharmacotherapy, and refused surgical bariatric procedures (endoscopic sleeve gastrectomy, RYGB)?	Almost never, Sometimes, Good portion (almost half) of the time, Most of my patients
How often do you encounter NASH patients with BMI>40 kg/m2 who failed the current standard of care noninvasive weight loss measures, including pharmacotherapy, and are not surgical candidates for surgical bariatric procedures?	Almost never, Sometimes, Good portion (almost half) of the time, Most of my patients
How often do you discuss with the patients in questions # 7 and # 8 the non-surgical (endoscopic) bariatric options?	Almost never, Sometimes, Good portion (almost half) of the time, Most of my patients
If you are an advanced/therapeutic endoscopist and trained in bariatric procedures, how often do you get referral from surgeons for patients in questions # 7 and # 8 to evaluate for endoscopic bariatric procedures?	Almost never, Sometimes, All the time
If you are an advanced endoscopist and trained in bariatric procedures, how often do you get a referral from a hepatologist for patients in questions # 7 and # 8 to evaluate for endoscopic bariatric procedures?	Almost never, Sometimes, All the time
How often do you discuss endoscopic bariatric options with NASH patients with BMI 30-40 who failed the current standard of care noninvasive weight loss measures, including pharmacotherapy?	Almost never, Sometimes, Good portion (almost half) of the time, Most of my patients
What do you think is the barrier to referral for minimally invasive, endoscopic bariatric procedures evaluation in NASH patients? (multiple answers)	Lack of evidence and limited research, Unable to obtain insurance coverage, No available specialist who can perform endoscopic bariatric procedures in my group/hospital/referral circle, I don't think endoscopic bariatric procedures work in my opinion
If you are an advanced endoscopist, how often are you successful in obtaining insurance coverage for your NASH patient?	Almost never, Sometimes, Good portion (almost half) of the time, Most of my patients
Which endoscopic bariatric procedure would you recommend to your NASH patient?	Intragastric balloon therapy, Endoscopic sleeve gastroplasty, Other (insert free text)

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2476-C | DIGITAL THERAPEUTICS LEAD TO CLINICALLY SIGNIFICANT BODY WEIGHT LOSS IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

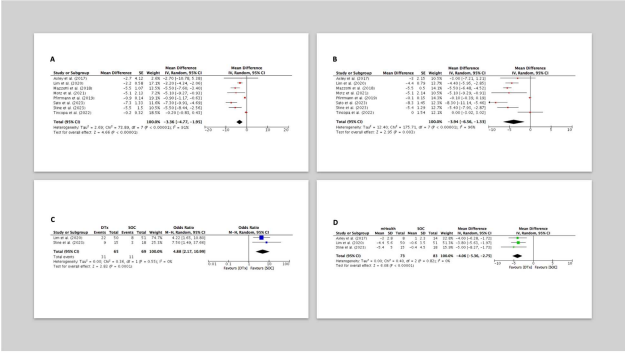
Somaya Albhaisi[1], Justin Tondt[2], John Cyrus[3], Rohit Loomba[4], David E Conroy[2], Vernon M Chinchilli[2] and Jonathan G. Stine[5], (1)Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA, (2) Penn State, (3)VCU, (4)University of California, San Diego, San Diego, CA, (5)Penn State Health Milton S. Hershey Medical Center, Hershey, PA, USA

Background: Lifestyle intervention remains crucial in the management of nonalcoholic fatty liver disease (NAFLD). However, most patients are unable to achieve clinically significant body weight loss with traditional in-person approaches. Digital therapeutic (DTx)-delivered interventions offer promise to remove barriers to weight loss success inherent to traditional in-person programs, but their efficacy remains relatively unknown. We aimed to determine 1) the pooled body weight loss of DTx lifestyle intervention programs and 2) whether DTx lifestyle intervention programs lead to greater body weight loss than standard of care (SOC). **Methods:** Published studies were identified by searching the following electronic databases: MEDLINE (PubMed) and Embase (Ovid).

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

The search criteria included publications through May 2023 with English language and human subject restriction. DTx intervention was compared to SOC. The primary outcome was change in body weight. Secondary outcomes included change in liver enzymes, liver fat, body fat, glycemic control and lipids. This study was registered on PROSPERO (42023420308). **Results:** Eight studies comprising 372 patients met inclusion criteria (mean age 47.3 y; BMI 33.2 kg/m^2). Mean body weight loss following DTx lifestyle intervention was -3.4 kg (95% CI -4.8, -2.0kg, $p < 0.01$) corresponding to -3.9% relative change (95% CI -6.6 to -1.3, $p = 0 < 0.01$). DTx lifestyle intervention was more likely to achieve body weight loss (absolute change -3.0 kg, 95% CI -4.3 to -1.8kg, $p < 0.01$, relative change -4.1%, 95% CI -5.4 to -2.8, $p < 0.01$) as well as clinically significant body weight loss of $> 5\%$ (OR 4.88, 95% CI 2.17-11.00, $p < 0.01$) than SOC. This was seen in parallel with reduction in liver enzymes, body fat, glycemic control and lipids. **Conclusion:** DTx-delivered lifestyle intervention programs lead to greater amounts of body weight loss than SOC, which uses a traditional, in-person resource-heavy approach. Clinically significant body weight loss with DTx was observed in parallel with improvement in routine clinical outcomes known to be important to patients with NAFLD, including those which surrogate for long-term outcomes. These results further support the role of DTx to deliver lifestyle intervention programs to patients with NAFLD and suggest that this scalable intervention offers promise to benefit the billions of patients worldwide who are living with NAFLD.

Figure 1- Pooled Efficacy of DTx in Leading to Body Weight Loss in Patients with NAFLD



A- Mean body weight loss with DTx is nearly 3.5 kg.
B- Mean relative body weight loss with DTx is nearly 4%
C- Subjects achieve 5% body weight loss or greater nearly 5x more often with DTx than SOC.
D- DTx leads to greater body weight loss than SOC.

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2477-C | DIY CLINIC: DEVELOPMENT AND IMPLEMENTATION OF A SUCCESSFUL NON-ALCOHOLIC FATTY LIVER WEIGHT MANAGEMENT CLINIC WITHIN THE VA

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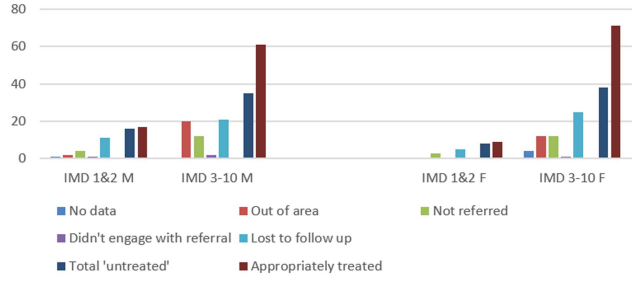
Background: 70% of patients with non-alcoholic fatty liver disease (NAFLD) have comorbid obesity. Intensive lifestyle counseling, anti-obesity medications (AOM) and bariatric surgery all have established benefits for patients with obesity. Less than 1% of patients eligible for antiobesity medications receive pharmacotherapy. We established a multi-disciplinary fatty liver weight loss clinic within the Washington, DC VA Medical Center to increase access to established obesity treatment in our NAFLD population. Here we describe the development of the program and early experience. **Methods:** Two hepatology providers collaborated with an obesity specialist to design a clinic format that would allow for multi-disciplinary management of patients with NAFLD and obesity. Patients were seen via telemedicine by a hepatology provider and jointly reviewed on a monthly basis by the entire clinician panel. As the clinic population grew a bariatric endoscopist and endocrinologists joined the multi-disciplinary discussion. Collaboration between the NAFLD clinician group and our dietician and pharmacy services streamlined access to AOM. Research collaborations were initiated by different members of the clinic panel. **Results:** From July 2022 to May 2023, 47 patients were seen in the fatty liver weight loss clinic. All patients were counseled on lifestyle changes and offered bariatric surgery referral if indicated. 38 (81%) patients were started

Background: Hepatitis B virus (HBV) is a global health problem with an estimated 200,000 individual's with chronic HBV in the UK, 95% of which are in immigrant populations. The goal of WHO HBV elimination by 2030 is challenging even in the UK partly because HBV is commoner in deprived areas, and a failure in investigation and referral pathways. The NHS England 'Core20Plus5' programme gives a mandate for tackling inequalities. 'Core20' refers to individual's in the 20% most deprived areas defined by the Index of Multiple Deprivation (IMD deciles 1 & 2). We tested the hypothesis that our novel case-finding database developed in Somerset (covering 0.6 million population) could identify HBV infected patients and provide means to target those in deprived areas. **Methods**: We configured our case-finding database to identify adult patients with HBV infection (positive HBV surface antigen). Within the tool, searches were stratified by IMD decile. Patients electronic records were reviewed to categorise as follows: 1) no data, 2) out of the area, 3) never referred, 4) never engaged following referral, 5) lost to follow-up (patient disengagement or system issues) and 6) actively followed or treated (chronic HBV or followed to surface antigen loss). Individual's in deprived areas data (IMD deciles 1 & 2) were compared to control (IMD 3 – 10). **Results**: Correcting for the known lower immigrant population we predicted 900 chronic HBV patients in Somerset (estimated 0.45% prevalence within the UK). The case finding database identified 302 HBV+ve patients. A deprivation score was available for 98.8% of the population. 9% of the whole Somerset population came from deprived areas compared to 24% of men and 12% of women with HBV ($P < 0.001$). Overall, 38% of patients with HBV were either not referred, didn't engage or subsequently lost to follow-up, and 97 patients were identified for further investigation/recall. There was a trend towards worse treatment rates in IMD 1 & 2 with 48% men and 47% women not appropriately engaged (Fig 1). **Conclusion**: HBV continues to be underdiagnosed with only 1/3 of expected patients identified in Somerset. This is likely to be multifactorial, including lack of screening of patients with abnormal LFTs and other risk factors. HBV is more common in deprived areas and our case finding database will now be used to target patients for treatment. In addition, it will be used to target individual's with persistently abnormal LFTs not previously tested for HBV.

Fig 1: Number of patients by referral & treatment category for deprived/not deprived; male/female



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2817-C | PRIVATE INSURANCE ACCESS IS ASSOCIATED WITH HIGHER LIVER TRANSPLANT LISTING AND TRANSPLANT ACCESS AND LOWER MORTALITY COMPARED TO NATIONAL INSURANCES IN A LARGE MULTI-NATIONAL COHORT OF INPATIENTS WITH CIRRHOSIS

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Background: Access to care in cirrhosis is based on insurance in most cases, which could be private (Pvt) or public based on individual centers/countries. However, the role of specific types of insurance on outcomes in a global cohort of cirrhosis inpts is unclear. **Methods**: The CLEARED Consortium enrolled cirrhosis inpts without COVID-19 who were followed during the admission & 30 days post-discharge. To ensure equity only 50 pts/site were allowed. Demographics, cirrhosis details, admission labs/drugds & hospital course were recorded. Outcomes were mortality & liver transplant (LT) in-hospital & 30 days post-discharge. Centers with predominantly public vs Pvt insurance were compared. Multi-variable analysis for LT & mortality was performed. **Results**: 4238 pts from 104 centers across 6 continents were included. 3013 (71%) were public; rest Pvt. Pvt insurance pts (USA, India, & centers in Latin America, Africa & Asia) were younger, more likely to have prior hospitalizations, HRS, refractory ascites, HE, AKI and more likely NASH, alcohol but lower viral hepatitis cirrhosis etiologies (Fig A). Pvt pts had higher MELD, were more likely to be on NSBB, SBBPr, rifaximin, lactulose & diuretics & had higher MELD score. These pts had ↓liver/infection-related & ↑liver-unrelated admissions. Among liver-related, pvt insurance pts had more HE & AKI/electrolyte changes but lower anasarca & HBV flares vs public. Outcomes: Pvt insurance pts had lower length of stay (LOS), ↑ ICU, & in-hospital AKI. Similar inpt mortality but higher inpt LT in Pvt was seen. Discharge: Pvt pts were discharged at a higher MELD, had a higher readmission and lower lost to follow-up rate. ↑LT rate & ↓mortality at 30-days was seen in Pvt pts (Fig B). Multivariable analysis: *30D mortality* was ↓with Pvt vs public(OR 0.45, $p < 0.0001$), alcohol etiology (0.70,$p = 0.004$), LT listed (0.45, $p < 0.0001$) & HBV antivirals (0.67,$p = 0.02$) & ↑with admission infections (1.93,$p < 0.001$), ICU need(4.18, $p < 0.0001$), & high discharge MELD-Na (1.21, $p < 0.001$). *30D LT* conversely was ↑in Pvt vs public (OR 2.1, $p < 0.001$), LT listed (11.0,$p < 0.001$), liver-related admission (2.33,$p = 0.02$),lactulose (2.1, $p < 0.001$),ICU transfer(4.76,$p < 0.001$) & high discharge MELD-Na (1.04,$p < 0.001$) & ↓with admission infections(0.53,$p = 0.003$). **Conclusion**: In this large multi-national consortium, cirrhosis pts with access to Pvt insurance had a similar inpt mortality despite more advanced cirrhosis on admission versus centers with mostly public insurance. Pvt insurance was linked to ↓ LOS, & likely resultant ↑30-day readmissions vs public insurance. However, more pts with Pvt insurance were listed for LT, & got inpt & 30-days post-discharge lT. This translated into lower mortality independent of demographics, medications, & in-hospital course. Systematic differences in Pvt versus public insurance, especially related to LT access, should be accounted for in cirrhosis outcomes analysis.

Figure A	Private Insurance (n = 1225)	Public Insurance (n = 3013)	p - value
Age (Mean (Std))	54.97 (13.57)	56.62 (13.11)	<0.001
Sex (Male)	804 (65.6)	1907 (63.3)	0.15
Admission details			
MELD-Na (Median (IQR))	24 (17, 30)	20 (14, 26)	<0.001
HCV etiology	108 (8.8)	341 (11.3)	0.02
Alcohol etiology	559 (45.6)	1130 (37.6)	<0.001
NASH etiology	315 (25.7)	411 (13.6)	<0.001
HBV etiology	122 (10.0)	764 (25.4)	<0.001
Prior HE	392 (32.1)	737 (24.5)	<0.001
Prior Ascites	853 (69.8)	1849 (61.4)	<0.001
Prior Transplant Listing	167 (13.7)	234 (7.8)	<0.001
Hospitalized in the Past 6mos	687 (56.2)	1427 (47.4)	<0.001
Prior Hepatorenal Syndrome	126 (10.3)	103 (3.5)	<0.001
Infection-related Admission	229 (18.7)	658 (21.8)	0.02
Liver Related Admission	1050 (85.7)	2794 (92.7)	<0.001
Non-Liver Related Admission	116 (9.5)	133 (4.4)	<0.001
Admission Betablockers	424 (34.6)	904 (30.0)	0.003
Admission Lactulose	697 (56.9)	1090 (36.2)	<0.001
Admission Rifaximin	471 (38.5)	548 (18.2)	<0.001
Admission Diuretics	701 (57.2)	1558 (51.7)	0.001
Admission PPI	688 (56.2)	1130 (37.5)	<0.001
Admission Statins	155 (12.7)	275 (9.1)	<0.001
Admission SBP Prophylaxis	259 (21.2)	301 (10.0)	<0.001
Admission HBV Antivirals	119 (9.8)	638 (21.3)	<0.001
Hospital & Discharge course			
ICU Transfer	349 (28.6)	406 (13.5)	<0.001
In-hHospital AKI	482 (41.4)	920 (30.9)	<0.001
Brain Failure	146 (12.0)	368 (12.2)	0.82
Respiratory Failure	178 (14.6)	209 (7.0)	<0.001
Circulatory Failure	157 (12.9)	311 (10.3)	0.01
LOS (Median (IQR))	7 (4, 13)	10 (5, 16)	<0.001
30-day outcomes			
Disch. MELD-NA (Median (IQR))	21 (15, 28)	18 (13, 24)	<0.001
Lost to Follow-Up at 30 Days	217 (17.7)	708 (23.5)	<0.001
30-Day Readmission	332 (33.1)	558 (24.6)	<0.001

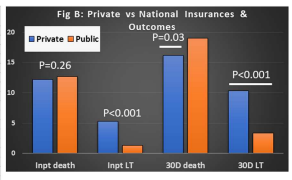

Figure A: Comparison between patients with centers with predominantly private versus national insurance

Figure B: Inpatient and 30-day outcomes: LT: liver transplant,30D: 30-days post-discharge

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2818-C | RACIAL DISPARITIES IN ADHERENCE TO FOLLOW-UP AND ACHIEVEMENT OF SUSTAINED VIROLOGIC RESPONSE IN PATIENTS INFECTED WITH HEPATITIS C: A TERTIARY CENTER STUDY AND OPPORTUNITIES FOR FURTHER INVESTIGATION

Clive Jude Miranda[1], Alexander Mark Carlson[2], Slah Khan[2], Farhan Azad[2] and Naren Srinath Nallapeta[2], (1) University at Buffalo, Buffalo, NY, (2)University at Buffalo

Background: Hepatitis C virus (HCV) is a worldwide public health and economic burden and is a leading cause of hepatocellular carcinoma, cirrhosis, and end stage liver disease. Despite the availability of efficacious and safe antiviral therapies, significant barriers still exist to achieving global eradication of HCV. Racial disparities exist among HCV treatment rates and adherence to follow-up. In the United States, most HCV patients are non-Hispanic Caucasians but roughly 3% of the black population is infected with HCV. Factors such as lack of access to healthcare, limited financial resources, and language barriers can all contribute to low treatment adherence rates among racial minorities. In our HCV tertiary care center, we aim to investigate race and its role in patient adherence to follow-up and achievement of sustained virologic response (SVR). **Methods:** A retrospective review of our institution's database was conducted from 2014 to 2022 for patients treated for HCV. Data collected included age, gender, race, and psychiatric comorbidities. Multiple logistic regression models were created to assess for statistical significance between demographic variables. Races were categorized as white, black (African/African American), Hispanic, and other. **Results:** A total of 1790 patients (66% male) between ages 20-89 being treated for HCV in our institution during 2014-2022 were identified. Racial breakdowns were 56% white, 31% black, 9% Hispanic, and 4% other. 1373 of these patients (77%) were compliant with follow-up, with a 95% SVR achievement rate observed in this cohort with no differences in race, age, sex, or language spoken. The remaining 417 patients (23%) were deemed non-compliant. Compliance was defined as being seen in our tertiary center over the past year or having achieved SVR. Non-compliance was defined as being lost to follow-up or not being seen in our institution over the past year. Of the non-compliant patients, racial breakdowns were 63% white, 21% black, and 8% Hispanic, and 8% other (Figure 1). An overwhelming majority of these patients were of poor

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status, and racial biases are factors that influence healthcare access and affect outcomes.
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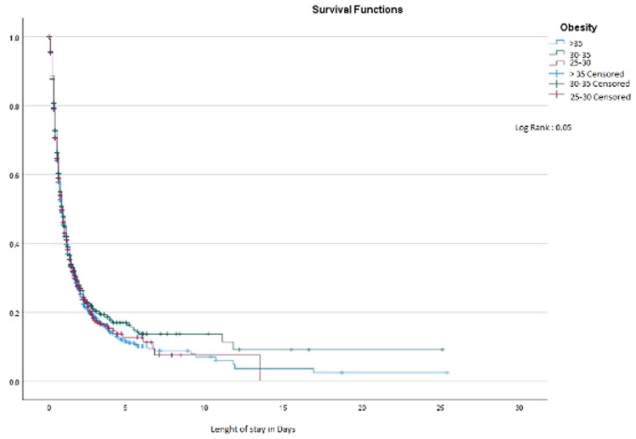
2851-C | THE TRIPLE BURDEN: HOW OBESITY AND LIVER CIRRHOSIS INFLUENCE PATIENT OUTCOMES, LENGTH OF STAY, AND HEALTHCARE COSTS"

Rajmohan Rammohan[1], Sai Greeshma Magam[1], Melvin Joy[2], Dilman Natt[1], Achal Patel[1], Abhishek Tadikonda[1], Jiten Desai[1], Sandra Gomez[1], Susan Bunting[1] and Paul Mustacchia[1], (1)Nassau University Medical Center, (2)Nassau University Medical Center, East Meadow, NY

Background: Liver cirrhosis is a significant public health issue in the United States, contributing to substantial morbidity and mortality rates. The prevalence of liver cirrhosis among US adults stands at 0.27%, which translates to 633,323 cases. Obesity is a well-established factor in the development of nonalcoholic fatty liver disease. Between 1999 and 2020, the obesity rate in the US population rose from 30.5% to 41.9%, while the prevalence of severe obesity increased from 4.7% to 9.2%. If obesity is not effectively addressed at an early stage, an inflammatory process begins within the liver, potentially leading to fibrosis and compromised liver function, ultimately resulting in cirrhosis. **Methods:** The Nationwide Inpatient Sample database was examined for the years 2019-2022, and data on 11,413 liver cirrhosis patients' hospital admissions were collected. Following propensity score matching, 5,097 patients were included in the study. Patients were categorized into three groups based on their BMI: Group A [>35] with 1,379 patients (27.1%), Group B [30-34] with 1,308 patients (25.6%), and Group C [25-29] with 2,410 patients (47.2%). Our study initially employed the Kaplan-Meier curve and Log Rank Mantel-Cox test to compare the three groups. Subsequently, we stratified the original dataset and applied the Hazard ratio to identify factors contributing to an extended length of stay. **Results:** A total of 5,097 liver cirrhosis patients were analyzed in this study. The median length of hospital stay, as determined by the Kaplan-Meier Curve, was 10 ± 5 days for Group A, 8 ± 4 days for Group B, and 3 ± 2 days for Group C. The Log Rank Mantel-Cox comparison among the three groups was statistically significant, with a p-value of 0.045. Factors that extended the length of hospital stay included abnormalities in COPD ($HR = 0.546$, $p < 0.01$), renal failure ($HR = 0.446$, $p = 0.04$), and heart failure ($HR = 0.716$, $p < 0.012$). Patients with more than two chronic diseases experienced a significantly longer stay ($HR = 0.746$, $p < 0.023$) compared to those without comorbidities. **Conclusion:** Obesity in liver cirrhosis patients, when accompanied by comorbidities, can impact the length of hospital stays. Factors contributing to extended stays can lead to increased healthcare costs.



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2852-C | UNDIAGNOSED CIRRHOSIS IN A NATIONAL COHORT OF VETERANS WITH DEMENTIA WITH POTENTIAL HEPATIC ENCEPHALOPATHY OVERLAP, IS HIGHER IN MINORITIES

Jasmohan S. Bajaj[1], Scott Silvey[2] and Nilang Patel[2], (1) Virginia Commonwealth University and Central Virginia Veterans Healthcare System, Richmond, VA, (2)Virginia Commonwealth University and Richmond VA Medical Center

Background: Dementia and hepatic encephalopathy (HE) can overlap given the increasing age of pts with cirrhosis. Within the Veterans Health Administration (VHA) patients in those with diagnosed cirrhosis, 8% have dementia with overlap with HE. HE is treatable, unlike dementia but only if suspected/identified. However, the rate of undiagnosed cirrhosis in those with dementia is unclear. **Aim**: Determine the rate and determinants of undiagnosed cirrhosis in Veterans with dementia **Methods**: Using the VHA Corporate Data Warehouse from 2009-2019, we identified pts with dementia at ≥ 2 time-points with validated codes. We then excluded pts with diagnosed cirrhosis & complications. The remaining pts were studied using the FIB-4 with > 3.25 and for sensitivity with a > 2.67 threshold. We collected AST/ALT values within 2 yrs after dementia diagnosis & capped the age at

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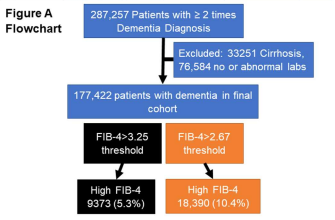
65 years to reduce confounding due to age. Crude comparisons: We compared demographics, co-morbidities [Charlson comorbidity index (CCI), organ dysfunction, diabetes, stroke, cardiovascular diagnoses], lifestyle (alcohol, tobacco), others (head injury, PTSD, depression) & hepatitis B/C. Multivariable logistic regression: 2 models were created using covariates that were significantly different; one for FIB-4 > 3.25 & one for > 2.67. **Results**: Of 287,257 patients with dementia, 38% were excluded for reasons shown in Fig A. Of the remaining 177422, 5.3% had FIB-4 > 3.25 while 10.3% patients had FIB-4 > 2.67. Crude comparison (Fig B): With > 3.25, high FIB-4 pts were more likely to be older, male, of Hispanic ethnicity and races other than White. High FIB-4 pts had higher alcohol use, HIV, hepatitis, & comorbidities such as hypertension, heart/kidney disease, PVD and stroke. In low FIB-4 pts, rural residence, tobacco use, diabetes, sleep apnea, head injury, depression and PTSD were higher. Similar trends were seen with > 2.67 cut-off. Multivariable regression: In the FIB-4 > 3.25 model, all variables were significant apart from head injury, sleep apnea, PVD, HIV, & Hispanic ethnicity (Fig C). In the FIB-4 > 2.67 model, all variables were significant, including Hispanic ethnicity but not sleep apnea, hypertension, head injury, & HIV. In both models, high FIB-4 scores were associated with CHF, hepatitis, alcohol use disorder, & male sex, while those with lowest odds ratios were white race, diabetes, tobacco use & hyperlipidemia. **Conclusion**: In Veterans with dementia without cirrhosis, we found undiagnosed cirrhosis in 5-10% of patients, the rate of which was higher in minorities. HE and dementia symptoms can overlap, therefore, missed cirrhosis could be associated with treatable HE that could improve symptoms and daily functioning. Determinants for undiagnosed cirrhosis were stable across FIB-4 thresholds. Clinicians encountering pts with dementia should focus on minorities, living in urban areas and with prior hepatitis and alcohol use, to ensure cirrhosis and potential HE is not missed

Figure B FIB-4 >3.25 threshold	High FIB-4 (n = 9373)	Low FIB-4 (n = 168049)	p-value
Demographics			
Age	80.78 (9.65)	78.21 (11.02)	<0.001
Male Sex	9211 (98.3%)	163148(97.1%)	<0.001
White race	8726 (75.2%)	129266 (80.4%)	<0.001
Hispanic ethnicity	654 (7.3%)	10872 (6.7%)	0.04
Rural residence	2601 (28.4%)	53387 (32.4%)	<0.001
BMI	25.78 (5.28)	26.73 (5.40)	<0.001
Co-morbidities			
Charlson comorbidity index	3.00 (2.00-5.00)	3.00 (2.00-5.00)	<0.001
Diabetes	3471 (37.0%)	65296 (38.9%)	<0.001
Hypertension	7511 (80.1%)	128989 (76.8%)	<0.001
Chronic kidney Disease	2584 (27.6%)	34529 (20.5%)	<0.001
Hyperlipidemia	7511 (80.1%)	128989 (76.8%)	<0.001
PTSD	1285 (13.7%)	26220 (15.6%)	<0.001
Depression	2237 (23.9%)	44618 (26.6%)	<0.001
HIV	66 (0.7%)	683 (0.4%)	<0.001
Hepatitis B/C	377 (4.0%)	3353 (2.0%)	<0.001
Head Injury	256 (2.7%)	6027 (3.6%)	<0.001
Alcohol Dependence	734 (7.8%)	10720 (6.4%)	<0.001
Tobacco Disorder	827 (8.8%)	15884 (9.5%)	0.04
Stroke	2142 (22.9%)	36923 (22.0%)	0.04
Peripheral vascular dz	1963 (20.9%)	29094 (17.3%)	<0.001
Congestive heart failure	3278 (35.0%)	42119 (25.1%)	<0.001
Sleep Apnea	1221 (13.0%)	24688 (14.7%)	<0.001

Figure C Variables	High in high FIB-4 OR (95% CI)	P value	Variables	Low in High Fib-4 OR (95% CI)	P value
Demographics					
Age	1.08 (1.06, 1.09)	< 0.001	White race	0.81 (0.75, 0.86)	< 0.001
Male sex	1.44 (1.28, 1.61)	< 0.001	BMI	0.97 (0.97, 0.98)	< 0.001
			Rural address	0.91 (0.86, 0.96)	< 0.001
Lifestyle					
Alcohol	1.37 (1.28, 1.46)	< 0.001	Tobacco	0.80 (0.71, 0.88)	< 0.001
Comorbidities					
Hypertension	1.10 (1.04, 1.16)	0.003	Diabetes	0.79 (0.74, 0.84)	< 0.001
CKD	1.53 (1.07, 1.19)	< 0.001	Hyperlipidemia	0.85 (0.80, 0.89	< 0.001
CHF	1.47 (1.42, 1.52)	< 0.001	Depression	0.94 (0.88, 0.99)	0.02
CCI	1.07 (1.05, 1.08)	< 0.001	PTSD	0.93 (0.86, 1.00)	0.03
Hepatitis	1.77 (1.65, 1.89)	< 0.001			



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2853-C | USING EXPLANATORY MIXED METHODS TO UNDERSTAND DISEASE-RELATED STIGMA AMONG KOREAN AMERICANS WITH CHRONIC HEPATITIS B (CHB)

Ann Klassen[1], Eunji Kim[1], Giyoung Lee[1], Katherine Clegg Smith[2], Hie-Won L. Hann[3], Mimi Chang[4], Ho Bae[4], Kyunghee Koh[5] and Hee-Soon Juon[5], (1)Drexel University Dornsife School of Public Health, (2)Johns Hopkins Bloomberg School of Public Health, (3)Thomas Jefferson University Hospital, Philadelphia, PA, (4) Coalition of Inclusive Medicine, (5)Thomas Jefferson University

Background: Stigma regarding infectious diseases is known to cause emotional distress, isolate individual's from their social networks, impact adherence and health outcomes, and undermine societal support for affected groups. However, it is less well understood how stigma is experienced differently within specific patient groups, and which patient groups should be prioritized for support. **Methods:** Our NIDDK-funded longitudinal cohort study, Bio-Psycho-Social Drivers of Disparities in Liver Disease Progression among Korean Americans with Hepatitis B Infection (MPI: Juon/Klassen), follows 365 patients at two clinical sites, collecting retrospective and prospective medical data, as well as structured surveys, in-depth qualitative interviews, hair cortisol biomarkers of chronic stress, and GIS-based analyses of neighborhood resources. This analysis focuses on survey responses to the HBQOL-Stigma subscale, and associations with psychosocial characteristics, including depressive symptoms and acculturative stress. A purposively selected subset of 30 participants is participating in 60-minute audio-recorded in-depth interviews, to elaborate qualitatively on patterns observed in the structured data. Thematic coding uses MAXQDA qualitative software, facilitating integration of quantitative and qualitative patterns. **Results:** The six-item, 30-point stigma index had strong reliability (alpha = 0.92), with a mean score of 5.4, and a range of 0-24. In a multivariable regression model, older age was significantly associated with lower self-reported stigma. Women as well as those with higher depressive symptoms and acculturative stress reported

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is proposed to be the time-window where critical interventions can be tried to change clinical outcomes of AKI. In cirrhosis, AKD and its impact on outcomes have been insufficiently evaluated. We aimed to investigate the incidence and clinical outcomes related to AKD in patients with cirrhosis and AKI. **Methods:** Cirrhotic patients, who were hospitalized from January 2014 to December 2017 at Daegu Catholic University Hospital, were assessed for AKI and AKD, and followed-up for 180 days. AKI, AKD and CKD were defined based on KDIGO and ADQI AKD and renal recovery consensus criteria, respectively. The primary outcome was mortality at 90 and 180 days, and the secondary outcome was de novo chronic kidney disease (CKD). **Results:** Of the 392 hospitalized patients with cirrhosis, AKI developed in 36.5% (n = 143). AKD occurred in 32.9% (n = 47) of AKI patients. The cumulative incidence of mortality was significantly higher in patients with AKD compared to to those without AKD: 90-day 12.8% vs. 61.7%, 180-day 17.7% vs. 68.8% ($p < 0.001$). On multivariable analysis, patients with AKD had higher risk of mortality at 90 dyas (hazard ratio [HR] 7.73; 95% CI 3.00-19.92; $p < 0.001$) and 180 days (HR 7.45; 95% CI 3.17-17.49; $p < 0.001$). The incidence of de novo CKD was 14.9% of AKD patients, but there was no occurrence of de novo CKD in patients without AKD. **Conclusion:** AKD develops in about 1 in 3 hospitalized cirrhotic patients with AKI and it is related to worse survival and de novo CKD.

Table1. Comparison of clinical characteristics between patients with and without AKD

Variables	No-AKD n=47	AKD n=47	*P* value
Age, years	52 (47-63)	58 (51-66)	0.196
Male, n (%)	30 (63.8)	39 (83.0)	0.036
Body mass index, kg/m^2	23.1 (20.225.2)	22.5 (21.0-25.0)	0.504
Diabetes, n (%)	16 (34.0)	17 (36.2)	0.829
Hypertension, n (%)	14 (29.8)	16 (34.0)	0.658
Chronic kidney disease, n (%)	2 (4.3)	7 (14.9)	0.080
Etiology of cirrhosis, n (%)			
Hepatitis B	7 (14.9)	4 (8.5)	0.336
Hepatitis C	2 (4.3)	4 (8.5)	0.399
Alcohol	40 (85.1)	42 (98.4)	0.536
Other	3 (6.4)	1 (2.1)	0.307
Liver-related complication at time of AKI			
Ascites	37 (78.7)	72 (89.4)	0.159
Spontaneous bacterial peritonitis (SBP)	1 (2.1)	8 (17.0)	0.226
Hepatic encephalopathy	11 (23.4)	20 (42.6)	0.048
Variceal bleeding	13 (27.7)	9 (19.1)	0.330
Non-SBP infection, n (%)	14 (29.8)	11 (23.4)	0.484
Baseline serum creatinine, mg/dL	0.8 (0.6-0.9)	0.9 (0.7-1.2)	0.019
MAP at time of AKI, mmHg	80 (70-90)	80 (70-90)	0.242
Laboratory findings at time of AKI			
White blood cell count, ×10^3/uL	10.7 (7.2-15.2)	8.6 (5.6-13.3)	0.441
Platelet count, ×10^3/ uL	77 (51-107)	85 (63-140)	0.043
Haemoglobin, g/dL	8.6 (7.1-10.7)	9.6 (8.4-11.0)	0.270
Sodium, mmol/L	130 (126-136)	132 (127-137)	0.752
Creatinine, mg/dL	1.8 (1.3-2.6)	1.6 (1.3-2.1)	0.437
Albumin, g/dL	2.8 (2.3-3.2)	2.5 (2.3-2.9)	0.383
Total bilirubin, mg/dL	3.9 (1.7-8.0)	4.4 (1.7-19.4)	0.010
INR	1.84 (1.58-2.14)	1.81 (1.35-2.24)	0.889
MELD-Na score at time of AKI	28.8 (21.8-34.4)	28.9 (23.8-33.3)	0.876
Child-Pugh score at time of AKI	9 (8-11)	10 (8-12)	0.358
Community-acquired AKI, n (%)	39 (83.0)	27 (54.7)	0.007
Stage of AKI at time of diagnosis, n (%)			
1	19 (40.4)	30 (63.8)	0.075
2	16 (34.0)	10 (21.3)	
3	12 (25.5)	7 (14.9)	
Peak AKI stage within 7 days post AKI			
1	16 (34.0)	12 (25.5)	0.654
2	14 (29.8)	15 (31.9)	
3	17 (36.2)	20 (42.6)	
Terlipressin use post AKI	17 (36.2)	14 (29.8)	0.510
Albnumin use within 7 days post AKI	7 (14.9)	13 (27.7)	0.131
ICU admission within 7 days post AKI	2 (4.3)	6 (12.8)	0.139
de novo Chronic kidney disease, n (%)	0 (0.0)	7 (14.9)	<0.001

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3002-A | ADIPOSE COMPARTMENTS PREDICT SEVERITY OF PORTAL HYPERTENSION AMONG PATIENTS WITH CIRRHOSIS

Mohammad S. Siddiqui[1], Danielle Kirkman[1], Vaishali Patel[2], Seung Lee[2], Jennifer Linge[3], Geneva Roche[1], Hiba Kamal[1], Per Widholm[3], Olof Dahlqvist Leinhard[4] and Mikael Fredrik Forsgren[4], (1)Virginia Commonwealth University, (2)Virginia Commonwealth University Health System, (3)Amra Medical AB, (4) Amra Medical

Background: Recent studies highlight the limited prognostic value of MELD score in cirrhosis and underscore the importance of developing additional multi-modal biomarkers. While skeletal muscle mass is a robust predictor of clinical outcomes in patients with decompensated cirrhosis, there is little data evaluating the relationship between other body compartments, such as adipose tissue, and portal hypertension. Thus, the aim of the current study was to evaluate the association between adipose tissue compartments and portal hypertension among patients with cirrhosis. **Methods:** 37 patients (29 females) with cirrhosis underwent 8-min magnetic resonance imaging (MRI) and blood work after an overnight fast. The MRI based assessment was measured via AMRA® Researcher and quantified body fat compartments that included abdominal subcutaneous adipose tissue (ASAT), liver fat content (LF), muscle fat infiltration (MFI) and visceral adipose tissue (VAT). MFI was adjusted for sex differences. Complications of portal hypertension included history of ascites, esophageal varices, acute variceal hemorrhage, hepatic encephalopathy, and spontaneous bacterial peritonitis. Mixed model linear regressions was used for statistical testing between body fat compartments and history of portal hypertension complications, etiology of chronic liver disease and gender. **Results:** The average MELD score of the study cohort was 13 and the most common etiology of cirrhosis was alcoholic and nonalcoholic steatohepatitis (n = 20). There was less body fat in those patients with a history of decompensation events when compared to patients who did not have a decompensating events (Figure 1). The data from linear regression models with standardized β-coefficient is as follows: MFI -2.62 pp ($p = 0.02$), VAT -2.57 L ($p = 0.01$), ASAT -3.35 L ($p = 0.06$), and liver fat -2.94 percentage points ($p = 0.03$). In addition to aggregate endpoint of presence of any decompensating event, an association between lower fat compartments and individual portal hypertension complications was also noted. The

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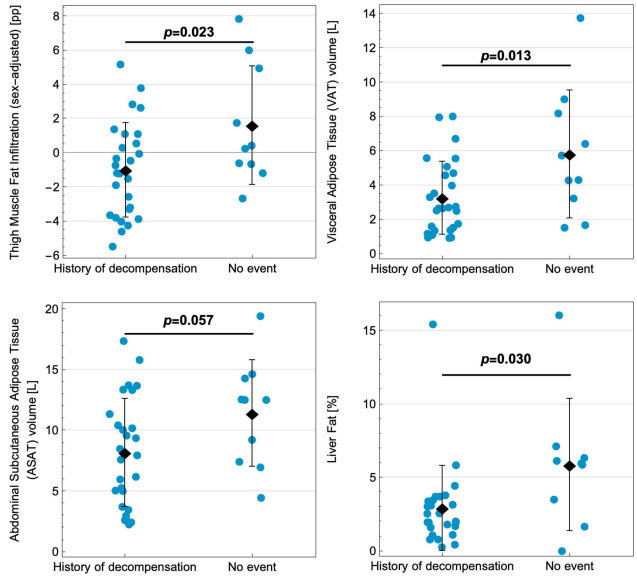
association between body compartments and previous portal hypertension complications was independent of gender and etiology of chronic liver disease leading to cirrhosis. In multivariate models all the fat compartments, including ASAT (p = 0.049), were significantly associated with presence of portal hypertension. **Conclusion:** The current study provides data demonstrating the relationship between portal hypertension related complications and lower adipose tissue depots. These findings have the potential to provide additional risk stratification tools in patients in whom the MELD score may not be as robust of predictor of clinical events. However, this requires further validation in well-designed prospective studies.



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3003-A | APPLICATION OF A FIB-4/VITRO SEQUENCE FACILITATES CACLD DIAGNOSIS AND RISK STRATIFICATION FOR SIGNIFICANT PORTAL HYPERTENSION WITHOUT NEED FOR LIVER STIFFNESS MEASUREMENT

Lukas Hartl[1,2], Georg Semmler[1,2], Mathias Jachs[2,3], Benedikt Simbrunner[4,5], Benedikt Silvester Hofer[5,6], Lorenz Balcar[2,7], Michael Schwarz[2,3], Laurenz Fritz[1], Anna Schedlbauer[1], Katharina Stopfer[1], Daniela Neumayer[1], Jurij Maurer[1], Robin Szymanski[1], Bernhard Scheiner[1,2], Michael Trauner[1], Thomas Reiberger[2,3] and Mattias Mandorfer[1,6], (1)Medical University of Vienna, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Vienna, Austria, (2) Medical University of Vienna, Vienna Hepatic Hemodynamic Lab, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Vienna, Austria, (3)Medical University of Vienna, (4)Cemm Research Center for Molecular Medicine of the Austrian Academy of Sciences, (5)Christian Doppler Laboratory for Portal Hypertension and Liver Fibrosis, Medical University of Vienna, (6)Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, (7)Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria

Background: The population at risk for liver-related complications is defined by compensated advanced chronic liver disease (cACLD), while presence of clinically significant portal hypertension (CSPH) identifies the target population for prevention of hepatic decompensation. Liver stiffness measurement (LSM) via vibration-controlled transient elastography enables non-invasive diagnosis of these conditions, but its availability is oftentimes limited to tertiary care, potentially impeding the identification of cACLD/CSPH in the community. Thus, we developed a routine laboratory-based algorithm to (i) identify patients with cACLD via fibrosis-4 index (FIB-4) and (ii) subsequently rule-in/rule-out CSPH using von Willebrand factor antigen/platelet count ratio (VITRO). **Methods:** FIB-4 cohort: To determine a FIB-4 cut-off for cACLD diagnosis, all patients with suspected cACLD undergoing LSM and FIB-4 assessment between 2007-2021 were characterized and followed-up for development of hepatic decompensation. VITRO cohort: cACLD patients (diagnosed by the FIB-4 cut-off) with hepatic venous pressure gradient (HVPG) measurement were analysed. **Results:** FIB-4 cohort: Among 6182 patients (median follow-up [FU] time: 54.6 mo) hepatic decompensation occurred in 3.4% (n = 211). Both LSM (AUC 0.90; 95%CI: 0.86-0.92) and FIB-4 (AUC 0.91; 95%CI: 0.88-0.94) exhibited excellent accuracy in predicting hepatic decompensation within 2 years of FU. FIB-4 ≥ 1.75 (corresponding to LSM ≥ 10kPa) was determined as cut-off for cACLD identification, ruling-out cACLD in 72% of patients. Patients with FIB-4 < 1.75 had negligible risk of of hepatic decompensation at 5 years of FU (cumulative incidence 0.03%). VITRO cohort: 317 cACLD patients (CSPH prevalence: 62.8%, n = 199/317) were included. Accuracy for diagnosing CSPG was similar for VITRO (AUC 0.85; 95%CI: 0.80-0.89), LSM (AUC 0.85; 95%CI: 0.81-0.89; DeLong-Test: p = 0.903) and the ANTICIPATE

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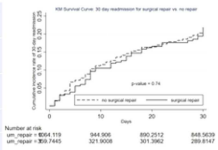
Table-1 Mortality and health care resource utilization

Outcomes	All cirrhosis (surgical repair vs. no repair)		Decompensated cirrhosis (surgical repair vs. no repair)		All cirrhosis (laparoscopic vs. open repair)	
	Effect estimate (95% CI)	p-value	Effect estimate (95% CI)	p-value	Effect estimate (95% CI)	p-value
In-hospital mortality (OR)	0.43 (0.16-1.18)	0.10	0.46 (0.08-2.61)	0.37	0.36(0.04-3.32)	0.36
Length of stay (β)	0.56(0.89-2.02)	0.44	7.66 (0.28-15.6)	0.05	1.88 (-4.49-0.73)	0.16
Hospitalization cost (β)	28597 (5296 – 51897)	0.02	112835 (2020-223650)	0.05	-31878 (64301-543	0.05
30-day readmission (HR)	1.26 (0.80 – 1.96)	0.32	0.62 (0.05-6.55)	0.69	0.49(0.15-1.56)	0.22



Disclosures: Mubeen Khan Mohammed Abdul – MedSys: Stock – privately held company (individual stocks and stock options), No, No;
The following people have nothing to disclose: Waseem Amjad, Kamran Safdar, Ajay Sahajpal, Sanjaya Kumar Satapathy

3027-A | PATIENT DEMOGRAPHICS, COMORBIDITIES, AND HOSPITAL CHARACTERISTICS OF HEPATORENAL SYNDROME

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Background: Hepatorenal syndrome (HRS) is a functional renal failure that develops as a consequence of decreased renal blood flow in patients with late-stage cirrhosis and ascites. The diagnosis requires combination of clinical observation and laboratory criteria. **Methods:** This is a retrospective study of the National Inpatient Survey (NIS) database of year 2020 including all adults age 18 and above with the discharge diagnosis of liver disease with and without hepatorenal syndrome. We identified the population with Chronic Liver disease with cirrhosis and Acute Kidney Disease with or without chronic kidney disease by searching the NIS database using the International Classification of Disease-10 (ICD-10). Inpatient mortality, morbidity, mean length of stay (LOS), mean total hospital charge (THC) and multivariate logistic regression, and linear regression analyses were used to analyze the data. **Results:** Out of 120,840 liver cirrhosis hospitalizations, 10,750 (8.9%) had developed hepatorenal syndrome. Patients with liver cirrhosis and hepatorenal syndrome had higher adjusted odds of inpatient mortality (Adjusted odds ratio [aOR]: 4.88, 95% confidence interval [CI]: 4.15-5.72, $p < 0.001$), longer mean LOS of 4.9 days (95% CI: 4.33-5.51, $p < 0.001$), and higher mean total hospital cost of $ 99255 (95% CI: 75731.6 - 122779.3, $p < 0.001$) than those without HRS. Out of all the patients admitted with cirrhosis, 5810 (4.8%) people died and in the subgroup with hepatorenal syndrome, 17.63% died ($P = 0.0000$). The OR for mortality in patients who develop hepatorenal syndrome is 5.8 [CI 5.06-6.64]. The mean length of stay in patients with HRS is 11.48 ± 0.36 days vs 5.34 ±0.5 days in patients without hepatorenal syndrome. The total cost of hospital stay was for patients with HRS was $192881 ± 15687 compared to those without which was $70293 ± 1796. The prevalence of sepsis in patients with HRS was 13.35% compared to those without which was 2.72% ($P = 0.000$), prevalence of mechanical ventilation was higher in the HRS subgroup at 6.98% vs 1.56% ($P = 0.0000$) and AKI prevalence in HRS was 89.58% vs 24.72% in HRS subgroup. ($P = 0.0000$) **Conclusion:** The patient with hepatorenal syndrome has in increased risk of mortality, longer days of hospital stay and higher hospital cost than those without. The risk of developing morbidities was also higher in the HRS subgroup.
Disclosures: The following people have nothing to disclose: Ayusha Poudel, Taha Teaima, Sajana Poudel, Eman Elhamamsy, Anurag Adhikari

3028-A | PATIENT SUBSET ANALYSIS OF THE REVERSE PHASE III STUDY: THE IMPACT OF TERLIPRESSIN TREATMENT ON RATES OF TRANSPLANT, DIALYSIS, AND SURVIVAL IN PATIENTS WITH HEPATORENAL SYNDROME

Samuel H. Sigal, Montefiore Medical Center and Albert Einstein College of Medicine, Arun Sanyal, Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA, Mark Wong, Banner University Medical Center, Brendan M. McGuire, University of Alabama at Birmingham, Birmingham, AL, Bilal Hameed, University of California San Francisco, San Francisco, CA and Khurram Jamil, Mallinckrodt Pharmaceuticals, Bridgewater, NJ

Background: Patients (pts) with untreated rapidly progressive hepatorenal syndrome (HRS) experience early mortality without liver transplantation (LT). Although HRS treatment can lower prioritization for LT due to a decrease in MELD score, a requirement for renal replacement therapy (RRT) is associated with poor survival. To determine the impact of terlipressin (terli) on LT and survival in pts with HRS, we analyzed data from the Phase lll, randomized, placebo (pbo)-controlled REVERSE study. **Methods:** A subset of US pts from the REVERSE study (excluding those with hepatocellular carcinoma, alcoholic hepatitis, or aged > 70 y) were analyzed ($N = 125$) by treatment group (terli, $n = 66$; pbo, $n = 59$). Pts were divided into the following groups by treatment response: HRS reversal (serum creatinine [SCr] ≤1.5 mg/dL), partial response (PR; SCr

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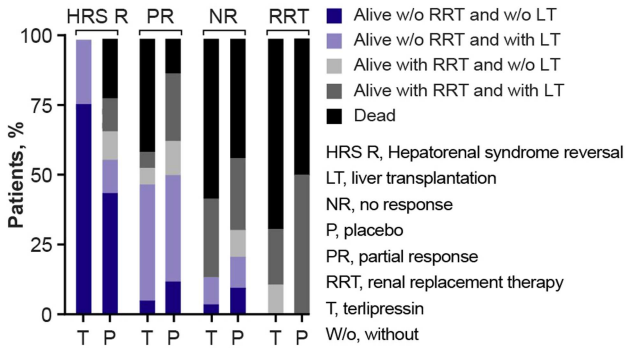
decreased > 0.3 mg/dL from baseline to end of treatment [EOT]), no response (NR), and those requiring RRT. The proportion of pts, (1) alive without RRT without LT, (2) alive with RRT with LT, (3) alive with RRT without LT, (4) alive with RRT with LT, or (5) dead, were assessed for each group at post-treatment Day 30, 60, and 90. Pts with HRS reversal were analyzed at the EOT for change in MELD score. **Results:** Reason for EOT: confirmed HRS reversal, 16.7% vs 15.3% ($P = 0.830$); RRT in 10.6% vs 11.9% ($P = 0.824$); EOT status: decrease in SCr, 31.8% vs 22.0% ($P = 0.220$); increase in SCr, 30.3% vs 37.3% ($P = 0.409$); for pts treated with terli and pbo, respectively. In pts with HRS reversal, survival without RRT at Day 90 was 100% for terli- and 55.6% for pbo-treated pts, respectively. Survival without RRT with/without LT progressively decreased in the PR and NR groups. Among those with RRT (n = 18), few pts were alive without LT at Day 90 (Figure). Baseline MELD scores were similar across treatment groups (mean [SD]: terli, 33.16 [6.16]; pbo, 32.67 [5.13]). HRS reversal was associated with decreased MELD scores (mean [SD]: terli, -4.4 [2.95] vs pbo, -5.6 [4.12]; $P = 0.5032$) from baseline to EOT. The incidence of LT at Day 30 was similar between the terli and pbo groups (30.3% vs 32.2%; $P = 0.819$). **Conclusion:** This post hoc subgroup analysis of pt data from REVERSE demonstrates clinical benefits among those who achieved HRS reversal and progressively worse outcomes for those with a PR or NR. Survival without LT is extremely limited for those who progress to RRT. Although MELD scores decreased with HRS reversal, overall LT rate was not adversely affected.

Figure. Clinical response at Day 90 by treatment response



Disclosures: Samuel H. Sigal – Mallinckrodt Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Mallinckrodt Pharmaceuticals: Consultant, Yes, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Consultant, No, No; Eli Lilly: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes;
Arun Sanyal – Durect: Stock – privately held company (individual stocks and stock options), No, No; GenFit: Stock – privately held company (individual stocks and stock options), No, No; Gilead: Consultant, No, No; Novartis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genetech: Consultant, No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Path-AI: Consultant, No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Histoindex: Consultant, No, No; Fibronest: Consultant, No, No; Hemoshear: Stock – privately held company (individual stocks and stock options), No, No; Hemoshear: Consultant, No, No; Inversago: Stock – privately held company (individual stocks and stock options), No, No; Biocellvia: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Eli Lilly: Consultant, No, No; Novo Nordisk: Consultant, No, No; Boehringer Ingelheim: Consultant, No, No; Astra Zeneca: Consultant, No, No; Boehringer Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Akero: Consultant, No, No; Intercept: Consultant, No, No; Fractyl: Consultant, No, No; Madrigal: Consultant, No, No; Northsea: Consultant, No, No; Takeda: Consultant, No, No; Regeneron: Consultant, No, No; Eli Lilly: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds),

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Mark Wong – Gilead: Speaking and Teaching, No, Yes;
Brendan M. McGuire – Mallinckrodt Pharmaceuticals: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), Yes, No; Arrowhead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, Yes; DISC: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
Bilal Hameed – CymaBay: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Gilead: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pliant Therapeutics: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Novo Nordisk: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Chronic Liver Disease Foundation (CLDF): Advisor, No, No; Pleiogenix: Advisor, No, No; Pioneering Medicine VII, Inc: Consultant, No, No; Pleiogenix: Stock – privately held company (individual stocks and stock options), No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Salix: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Mallinckrodt Pharmaceuticals: Advisor, Yes, No; Gilead: Consultant, No, No;
Khurram Jamil – Mallinckrodt Pharmaceuticals: Employee, Yes, No;

♦ 3029-A | Patients with Cirrhosis and Significant Ascites are At High Risk of Cirrhotic Cardiomyopathy

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Background: Cirrhotic Cardiomyopathy (CCM) entails alternations of cardiac structure and function among patients with cirrhosis in the absence of alternative cardiac pathology. CCM criteria were revised in 2020 reflecting advancement in echocardiographic technology. Prior studies showed an association of refractory ascites with decreased cardiac output and hemodynamic changes. However, data are lacking regarding the impact of ascites on cardiac function assessed by contemporaneous echocardiographic markers. This study aims to evaluate the association of hepatic ascites with CCM and its echocardiographic markers per 2020 criteria. **Methods:** We performed a retrospective cohort study of adult

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

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Background: Recombinant human albumin (rHA) is an alternative to human serum albumin (HSA) for the management of ascites in cirrhotic patients. This phase II study was designed to evaluate dose effect, safety and immunogenicity of rHA injection in treatment of hypoalbuminemia in cirrhotic patients with ascites. It is to provide the basis for the design of Phase III clinical trial. **Methods:** This multicenter, blinded, positive controlled, phase II/III, adaptive design and seamless connection study enrolled 90 Chinese subjects divided into two dose cohorts(Figure 1). Each cohort included 45 subjects who were randomized 2:1 to receive rHA or HSA, respectively, at a dose of 10 g/day (14 d of administration) or 20 g/day (7 d of administration). All subjects were followed-up for 56 days after the treatment was concluded. The primary objective was to assess the initial efficacy, dose effect, safety and immunogenicity of rHA. Efficacy was assessed by monitoring serum albumin concentration and plasma colloid osmotic pressure (PCOP) before and after each dose of rHA or HSA. The time required for the serum albumin concentration to reach 35 g/L was also monitored. Safety was determined by the incidence, intensity, and seriousness of adverse events. **Results:** Improvement of serum albumin concentration in the rHA cohorts was similar to that in the HSA cohorts during both treatment and follow-up. In two dose groups, the increase of the serum albumin level and PCOP in 20 g/d group were faster than those in 10 g/d group. The incidence of adverse events was similar between the rHA and has cohorts, and no dose-response relationships were observed for adverse events. No anti-drug antibodies were found in an immunogenicity study. **Conclusion:** The efficacy and safety of rHA injection (the investigational drug) was basically the same with HSA (the control drug) in two dose groups (CTR20212001). The results of this clinical trial support the investigational drug to enter Phase III study. Since 20 g/d group has the same safety risk as 10 g/d group, and 20 g/d could increase the level of albumin and PCOP more quickly than 10 g/d, the dose of 20 g/d was recommended for Phase III study.

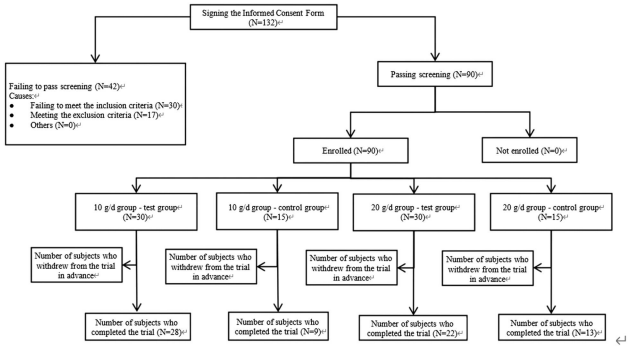

Figure 1. Flow chart of subject disposition

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The following people have nothing to disclose: Xu Li, Yanhang Gao, Xinrui Wang, Wanyu Li, Yanjun Cai, Runping Gao, Yu Pan, Qinglong Jin, Dachuan Cai, Bin Xu, Yulin Hu, Xiaofeng Wu, Xiaolin Guo, Xiaoping Wu, Xiangjun Jiang, Zhenjing Jin, Guangming Xiao, Jidong Jia, Wen Xie, Junqi Niu

3057-A | A NOVEL SWEAT SENSOR DETECTS INFLAMMATORY BIOMARKERS IN INPATIENTS AND OUTPATIENTS WITH CIRRHOSIS

Brian C. Davis[1], Kevin Lin[2], Andrew Fagan[3], Michael Fuchs[4], Puneet Puri[5], Mary Leslie Gallagher[6], Travis Mousel[3], Shalini Prasad[7], Sriram Muthukumar[2] and Jasmohan S. Bajaj[8], (1)Hunter Holmes McGuire VA Medical Center, (2)Enlisense Inc, (3)Virginia Commonwealth University and Richmond VA Medical Center, (4)Mcguire Veterans Affairs Medical Center, Moseley, VA, (5)Virginia Commonwealth University, (6) McGuire Veterans Affairs Medical Center, (7)University of Dallas, (8)Virginia Commonwealth University and Central Virginia Veterans Healthcare System

Background: Biomedical sensing, especially related to inflammatory markers, could increase insight into cirrhosis-related complications. Sweat sensing using the AWARE sensor could be used to monitor minute-by-minute changes in inpts/outpts with cirrhosis, which is a non-invasive monitoring modality. Aim: Define relationship of serum and sweat inflammatory markers in cirrhosis. **Methods**: Inpatients or outpatients with cirrhosis underwent AWARE sensor application daily for up to 3 days (Fig A). Daily blood CRP, IL-6 &TNF measurements were performed and compared with sweat values of these analytes. Serum value at each blood draw & sweat time-weighted average values of analytes were compared between inpts & outpts and correlated with each other. Blood IL-6/TNF were analyzed using ELISA while blood CRP was sent to our clinical lab. Quality of life using Sickness Impact Profile (SIP: high = worse with physical and psychological domains) was studied. Correlations between sweat & serum analytes with MELD-Na and SIP scores were performed. **Results**: 32 pts (10 outpt/22 inpts) were included. All outpts were seen for 3 days, while 13 inpts were seen for 2 days and 7 for 3 days with daily blood draws. Day 1 data, which was available on everyone, was analyzed and is presented. All inpts were admitted

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for cirrhosis-related complications (14 with infections, 8 with AKI/electrolyte issues, 8 with hepatic encephalopathy, 5 with ascites) and had mean Length of stay of 5.5 ± 0.81 days. 12 were on antibiotics. MELD score and all inflammatory markers were higher in inpts over several days (Fig B). SIP total/physical were higher in inpts. Correlation of sweat and serum IL-6, TNF & CRP were highly significant across groups, even though the values were higher in inpts (Fig C-E). This pattern was also seen in sweat and serum comparisons, which showed that regardless of the fluid tested, inpts had higher concentrations (Fig F-H). Correlations between MELD-Na, Total SIP, Physical SIP & the analytes showed that SIP & Physical SIP were only correlated with sweat CRP but not blood CRP, while the opposite pattern was seen with IL-6 and TNF, where blood values were more correlated. Both CRP in blood and serum were linked with MELD-Na but only blood TNF and IL-6 and not sweat levels were linked with MELD-Na (Fig I) **Conclusion**: We showed good correlation between sweat and serum values of CRP, IL-6 and TNF in outpatients and inpatients with cirrhosis. Values of both sweat and serum analytes were higher in inpatients compared to outpatients. Quality of life was significantly linked with sweat CRP but not serum CRP but the opposite pattern was seen with IL-6 and TNF. CRP values, regardless of serum or sweat, were linked with the MELD-Na. The differential linkage of sweat CRP to quality of life may be a novel pattern to evaluate for long-term management of these patients. The AWARE sensor is feasible in inpatients and outpatients with cirrhosis and show similar patterns to blood levels of CRP, IL-6 and TNF.

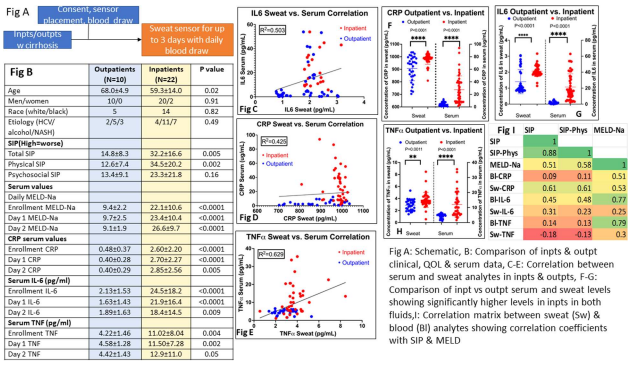

Fig A: Schematic, B: Comparison of inpts & outpt clinical, QOL & serum data, C-E: Correlation between serum and sweat analytes in inpts & outpts, F-G: Comparison of inpt vs outpt serum and sweat levels showing significantly higher levels in inpts in both fluids,I: Correlation matrix between sweat (Sw) & blood (Bl) analytes showing correlation coefficients with SIP & MELD

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3058-A | A PROSPECTIVE STUDY EVALUATING THE PREVALENCE AND SEVERITY OF PSYCHIATRIC DISORDERS IN PATIENTS WITH CIRRHOSIS OF LIVER AND AT 3months FOLLOW UP DURING THE EARLY POST COVID ERA

Ameet Mandot, Global Hospitals, Mumbai and Vishal Ramchandra Shriwastav, Bombay Hospital and MRC

Background: Psychiatric disorders (depression, anxiety, stress) are frequently observed in patients with cirrhosis of liver and significantly impact their overall health outcomes. Mental health evaluation in chronic diseases is not given enough importance in a developing country like India with burdened healthcare system. There have been few studies of their prevalence among patients with cirrhosis of liver in pre COVID and COVID era. However the data on prevalence of psychiatric disorders in cirrhotics in early post COVID era is limited and also the progression of pyschiatric diseases with progression of cirrhosis is not well studied. We aimed to characterize the prevalence of psychiatric disorders: depression, anxiety and stress in cirrhosis of liver at presentation and their association with MELD-NA score at 3 months during the early post COVID era. **Methods:** We performed a prospective study with sample size of 135 indoor and OPD patients with newly diagnosed cirrhosis from March 2022 to March 2023 at a single tertiary care private hospital in

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3060-A | A SPECIALIZED HEPATIC ENCEPHALOPATHY TESTING CLINIC IMPROVES RATIONAL DECISION MAKING FOR HE THERAPY AND CAN DETECT ALTERNATIVE CAUSES FOR COGNITIVE IMPAIRMENT IN CIRRHOSIS

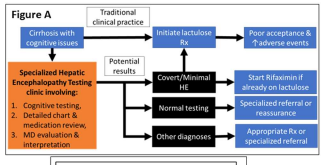
Asiya Tafader[1], Mahum Nadeem[1], Dan Park[1], Andrew Fagan[1], Brian C. Davis[1], Michael Fuchs[2], Puneet Puri[3], HoChong Gilles[4], Jennifer Miller[4], Felicia Tinsley[1] and Jasmohan S. Bajaj[5], (1)Virginia Commonwealth University and Richmond VA Medical Center, (2) Mcguire Veterans Affairs Medical Center, Moseley, VA, (3)Division of Gastroenterology, Hepatology, and Nutrition, Richmond VA Medical Center, Richmond, VA, (4)Mcguire Richmond VA Medical Center, (5)Virginia Commonwealth University and Central Virginia Veterans Healthcare System

Background: Cognitive impairment in cirrhosis could have many underlying causes but most are presumed to be hepatic encephalopathy (HE) & are reflexively treated (Fig A) with either lactulose (difficult to tolerate) or rifaximin (expensive). Moreover, many pts may not have HE as the cause for these symptoms. Most pts are not routinely tested for minimal HE(MHE) and the utility of on-demand MHE testing/interpretation in clinical settings needs to be studied. **Methods**: We set up an on-demand standard of care HE testing clinic (Fig A). Pts were tested separately from their original clinic visit for cognitive issues elicited by clinicians, pts or caregivers. The clinic involves specialized testing (Mini-mental status exam [MMSE out of 30, >25 = no dementia, psychometric hepatic encephalopathy score (PHES) & EncephalApp Stroop] by a trained medical assistant, Results were interpreted by a hepatologist after chart/medication review and recommendations were noted in the record and sent to referring clinicians. Time spent on testing/interpretation and for the medical decisions made were recorded. **Results**: From 2012-2022, 282 mostly male pts were evaluated, majority (84%) were due to cognitive complaints by pts/families. Of the patients referred, four had MMSE <25, which were then referred for dementia evaluation without further tests.

No-MHE patients: 111 (39%) had normal cognitive performance (Fig C). These pts (Fig B) were younger, less likely to have prior HE, depression, lower MELD-Na, and ascites vs who tested impaired. Anxiety, chronic pain, gender, etiology, & race were similar. *Action for no-MHE pts*: Most (N = 84) were reassured of their normal results & did not need lactulose. The rest, were referred to other specialties if requested.

Cognitively-impaired: We continued current Rx, i.e. no therapy because the pt refused or continued same HE regimen in 47(17%). Of the rest, 56 (20%) were initiated on lactulose, & 27 (10%) were started on rifaximin. The remaining 37 pts were judged to have issues unrelated to cirrhosis as the major contributor(s) to their cognitive impairment. These were related to pain medications, obstructive sleep apnea, dementia, and neuro-modulator therapy, for which they were either referred to their primary care doctors, neurologists, or pain management.

Time needed: Medical assistant took 34 ± 12 min/pt. The hepatologist took 12 ± 5 min to interpret & complete the recommendations, which were billed for. **Conclusion**: A dedicated US-based HE testing clinic run by a trained medical assistant and supervised by an attending reduced reflexive HE therapy initiation in the majority of patients. On specialized testing that <40 minutes to perform & interpret, and which was billable, 39% pts showed normal cognition & were spared reflexive lactulose. 14% pts needed referral for other neurocognitive issues & only 30% needed HE therapy change, or initiation. Dedicated HE testing clinics may be effective in streamlining HE management.



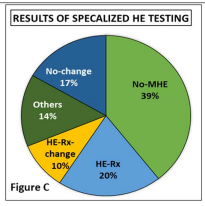


Figure B

	Cognitive impairment (N=172)	No cognitive impairment (n=110)	P value
Age	60.7±6.9	57.8±8.9	0.005
Male Gender	165	105	0.95
Caucasian race	106	67	0.83
Etiology (Alcohol/ HCV/NASH/Mixed /Others)	41/51/25/44/11	20/47/15/19/10	0.15
Prior ascites	69	26	0.003
Prior HE	66	8	<0.0001
History of varices	62	30	0.008
Prior SBP	14	0	<0.0001
Anxiety	17	8	0.44
Depression	48	19	0.03
Chronic pain	41	29	0.65
Non-selective beta-blockers	69	29	0.02
Labs			
Platelet count	125±71.2	149.9±74.6	0.006
Creatinine	1.09±0.43	1.05±0.32	0.42
INR	1.34±0.41	1.29±0.60	0.38
Bilirubin	2.04±2.76	1.32±1.64	0.007
Sodium	137.9±3.8	138.6±2.8	0.09
Albumin	3.22±0.70	3.48±0.68	0.002
MELD-Na	13.51±6.31	10.92±3.79	0.03
Dedicated testing			
MMSE (of 30)	28.33±1.71	29.08±0.99	<0.0001
PHES (5 to -15, high=good)	-6.65±3.95	-1.08±2.44	<0.0001
Stroop Off+On Time (low=good)	228.3±88.5	175.7±42.6	<0.0001

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The following people have nothing to disclose: Asiya Tafader, Andrew Fagan, Brian C. Davis, Puneet Puri, HoChong Gilles, Michael Fuchs
Disclosure information not available at the time of publication: Mahum Nadeem, Dan Park, Jennifer Miller, Felicia Tinsley

3061-A | ALCOHOL AGGRAVATES NEUROLOGICAL DYSFUNCTION AND LEADS TO PERMANENT CELL INJURY IN RATS WITH CHRONIC LIVER DISEASE

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Background: Hepatic encephalopathy (HE) is a debilitating neurological complication of chronic liver disease with alcohol being a common etiological factor. However, excessive alcohol consumption has been shown to impact neurological integrity. To date, the influence of alcohol in the development of HE remains unclear. Therefore, we examined the effect of constant alcohol consumption on neurological decline in rats with chronic liver disease induced via bile-duct ligation (BDL). **Methods:** 6-week BDL rats and Sham-operated controls were used. Day 7 after surgery, rats were administered Alcohol (51% v/v Ethanol) twice a day (dose of 3g/kg, via gavage) for 4 weeks. Motor coordination (rotarod) and anxiety-like behavior (open field (OF) and elevated plus maze (EPM)) were assessed at day 40. Upon sacrifice, brains were collected, and western blot and immunohistochemical (IHC) analyses were used to investigate neuronal integrity in frontal cortex and cerebellum. **Results:** Alcohol further impaired motor coordination in BDL rats when compared to SHAM-Alcohol ($p < 0.01$). Furthermore, BDL-Alcohol rats demonstrated an increase in anxiety-like behavior; increase in time spent in the closed arms of EPM and decrease in time spent in the center of the OF ($p < 0.05$ vs SHAM-Alcohol). BDL-Alcohol rats demonstrated a decrease in neuronal markers of NeuN and SMI311 ($p < 0.01$ and $p < 0.05$, respectively), an increase in apoptotic markers of cleaved/pro-caspase3 ($p < 0.001$), an increase in necroptosis markers of pRIP3 and pMLKL ($p < 0.01$ and $p < 0.001$, respectively), a decrease in total antioxidant capacity ($p < 0.001$) and an increase in oxidative stress marker of 4-HNE ($p < 0.05$) in the cerebellum (not found in frontal cortex) compared to all groups. IHC results confirmed the colocalization of apoptotic marker (cleaved Caspase3) and necroptosis marker (pMLKL) in the granular and Purkinje layer neurons of the cerebellum of BDL-Alcohol rats. **Conclusion:** Constant alcohol consumption exacerbates HE and leads to neuronal loss via apoptosis and necroptosis in the cerebellum. Additionally, higher levels of oxidative stress marker of 4-HNE and decreased total antioxidant capacity in the cerebellum of BDL-Alcohol rats suggest that oxidative stress is a triggering factor leading to neuronal loss/injury. These results demonstrate an adverse effect of constant alcohol consumption on the development of HE and neuronal integrity in chronic liver disease.
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3062-A | ANALYSIS OF RELEVANT FACTORS OF PORTAL VEIN THROMBOSIS IN LIVER CIRRHOSIS

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Background: To investigate the usefulness of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), protein C (PC), and thromboelastography (TEG) to serve as a predictor of portal vein thrombosis (PVT) in patients with liver cirrhosis. Additionally, we examined the clinical signifcance of the above indicators in terms of disease progression. **Methods:** A total of 123 patients with liver cirrhosis were recruited from May 2021 to December 2021, according to the imaging fndings. They were divided into the PVT group ($n = 52$) and the non-PVT group ($n = 71$). Furthermore, patients with PVT were divided into plasma transfusion groups ($n = 13$) and non-plasma transfusion groups ($n = 39$).

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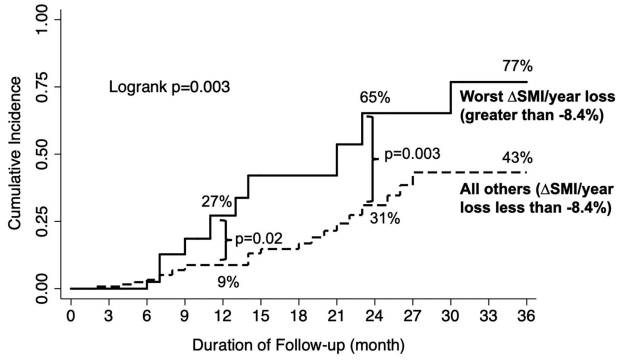
rapid muscle loss was independently associated with higher waitlist mortality. Our data are essential for determining the effect size necessary to adequately power clinical trials targeting therapeutic interventions aimed at improving muscle mass in this population.

Figure. Cumulative incidence of waitlist mortality through 36 months according to change in skeletal muscle index by ΔSMI/year (%) loss



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The following people have nothing to disclose: Nghiem B. Ha, Bo Fan, Amy M. Shui, Chiung-Yu Huang

3067-A | DETERMINING CLINICALLY MEANINGFUL DIFFERENCE IN BASELINE ENCEPHALAPP STROOP VALUES TO PREDICT HE-RELATED OUTCOMES WITH MULTI-CENTER VALIDATION

Gowthami Kanagalingam[1], Dan Park[2], Bryan Badal[3], Andrew Fagan[2], K Rajender Rajender Reddy[4], Jacqueline G. O'Leary[5], Jennifer C. Lai[6], Puneeta Tandon[7], Florence Wong[8], Patrick S. Kamath[9], Guadalupe Garcia-Tsao[10], Scott W. Biggins[11], Hugo E. Vargas[12], Chathur Acharya[13] and Jasmohan S. Bajaj[2], (1)Virginia Commonwealth University, (2)Virginia Commonwealth University and Richmond VA Medical Center, (3)Virginia Commonwealth University and Richmond VA Medical Center, Richmond, VA, (4) University of Pennsylvania, (5)Utsw, Dallas, TX, (6) University of California-San Francisco, San Francisco, CA, (7)University of Alberta, AB, Canada, (8)Toronto General Hospital, Toronto, ON, Canada, (9)Mayo Clinic, Rochester, MN, (10)Department of Digestive Diseases, VA - CT Healthcare System, (11)University of Washington, Seattle, WA, (12)Mayo Clinic Arizona, Phoenix, AZ, (13)Ohio State University Wexner Medical Center

Background: EncephalApp Stroop is a simple method to diagnose minimal hepatic encephalopathy & is linked with overt HE (OHE), & hospitalizations. Aim: (i) define Stroop OffTime+OnTime completion time test/retest variation and baseline differences in this completion time that would predict increased risk of OHE/hospitalizations over time & (ii) to validate this time difference in a second cohort. **Methods**: 3 prospective cohorts were enrolled: *Cohort 1:* Stroop at baseline then followed till OHE/hospitalization or last clinical outcome available from 2 centers (University+VA), *Cohort 2*: Test/retest cohort from University+VA & *Cohort 3:* Multi-center cohort followed for 3 mths. OffTime+OnTime was used as Stroop outcome (Fig A).
Cohort 1: Baseline cirrhosis details, co-morbidities & medications were collected. Stroop values were studied using Cox proportional hazards with OHE/hospitalization as primary outcomes. Baseline Stroop values between those who developed OHE/hospitalization sooner vs rest were compared unadjusted & adjusted for clinical variables.
Cohort 2: A separate group underwent Stroop twice without underlying clinical change.
Cohort 3: Cirrhosis outpts from 10 N American sites underwent Stroop & were followed for 3 mths for OHE-related hospitalizations. Baseline adjusted/unadjusted Stroop differences were compared to cohort 1. **Results**: 2-center cohort: 278 pts (62 y, 96% men, MELD-Na 11, 33% prior OHE, 41% ascites) were followed for a median of 7 (3,24 IQR) mths. 16% developed OHE & 12% OHE hospitalization at a median of 6 & 3 mths post-testing respectively. On Cox Proportional hazards for OHE, Stroop time $p = 0.002$, MELD-Na $p < 0.0001$ & ascites $p = 0.003$, were significant; similar variables (Stroop $p < 0.001$, MELD-Na $p = 0.009$, Ascites $p = 0.03$ & beta-blockers $p = 0.04$) were significant for OHE hospitalization. Prior HE, meds & demographics were not linked. After adjusting, we found significant baseline Stroop differences between those that developed outcomes/not (Fig B).
Test-retest cohort: 44 pts (66 y, 42 men, MELD-Na 10, Prior OHE 25%, 34% ascites) received Stroop

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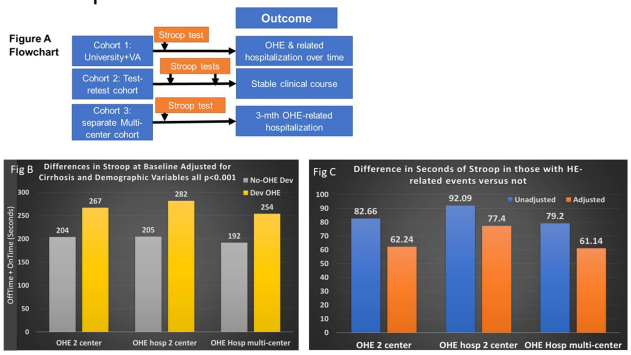
twice a median of 13 (4-24) mths apart without significant change in OffTime+OnTime (212.4 ± 65.1 vs 210.44 ± 79.9 sec, p = 0.75)

Multi-center cohort: 357 pts (59 y, 69% men, MELD-Na 15, Prior OHE 38%, 73% ascites) were recruited from 10 sites. 14 (4%) developed 3-mth OHE hospitalizations, who were more likely to have prior OHE & higher MELD. Despite the cohort differences (outcome numbers, patient details & f/u duration), we found similar adjusted Stroop baseline differences in pts with/without OHE development (Fig C).

Conclusion: In this prospective study with multi-center validation, we found that > 60 second OffTime+OnTime difference on Stroop portended an increased risk of OHE & related hospitalizations over median 7 months, which is higher than test/retest variations. Baseline Stroop time differences may add to OHE risk prediction over simple clinical models.



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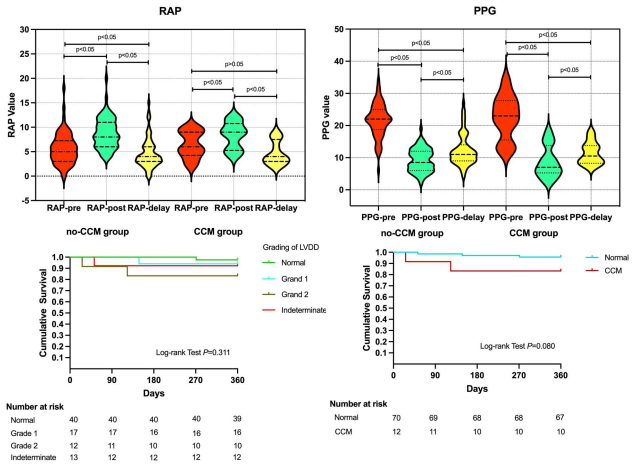
3068-A | DIASTOLIC DYSFUNCTION IN CIRRHOTIC CARDIOMYOPATHY: A PROSPECTIVE OBSERVATIONAL COHORT STUDY ON SHORT-TERM OUTCOMES IN CIRRHOTIC PATIENTS UNDERGOING TIPS

Yaozu Liu[1,2,3], Fangmin Meng[1,4], Wen Zhang[1,2,3], Jingqin Ma[1,2,3], Zhiping Yan[1,2,3], Cuizhen Pan[1,4] and Jianjun Luo[1,2,3,5], (1)Shanghai Institute of Medical Imaging, (2)Department of Interventional Radiology, Zhongshan Hospital, Fudan University, (3)National Clinical Research Centre for Interventional Medicine, Zhongshan Hospital, Fudan University, (4)Department of Echocardiography, Zhongshan Hospital, Fudan University, (5)Centre for Tumor Diagnosis and Therapy, Jinshan Hospital, Fudan University

Background: The placement of Transjugular intrahepatic portosystemic shunt (TIPS) results in a sudden increase in central circulating blood volume, which requires proper regulation of the cardiovascular system. The presence of diastolic dysfunctional cirrhotic cardiomyopathy indicates myocardial dysfunction which may lead to adverse outcomes in patients treated TIPS. However, data regarding population primarily affected by hepatitis B virus (HBV) infection remains limited. Furthermore, impaired cardiac function may influence portal pressure gradient (PPG) and right atrium (RA) pressure measurements, potentially influencing the efficacy of TIPS. The aim of our study was to investigate the impact of diastolic dysfunction on TIPS. **Methods:** A consecutive case series of patients with cirrhosis aged 18-65 years who underwent TIPS were prospectively studied. Left ventricular (LV) filling pressure was evaluated using four criteria based on the algorithm proposed by the Cirrhotic Cardiomyopathy Consortium (CCC). Patients with systolic dysfunction (defined as LVEF $\leq$ 50% or LV GLS absolute value $<$ 18%) were excluded from the study to eliminate the effects of systolic dysfunction. All participants were followed up for at least one year post-TIPS, with the primary study endpoint being all-cause mortality following the procedure. **Results:** From June 2020 to January 2022, 82 patients were included. According to the Cirrhotic Cardiomyopathy Consortium (CCC), 48.8% had no LVDD, 20.7% had grade 1, 14.6% had grade 2 (CCM), and 15.9% were indeterminate. The incidence of diastolic dysfunctional CCM is 14.6% in our study. The results indicate that RAP increased after TIPS and returned to baseline after 48 hours in patients with CCM (4.63 ± 2.46 VS 6.42 ± 2.75 $p = 0.076$). In contrast, patients without CCM had lower RAP than baseline after 48 hours (4.63 ± 3.05 VS 5.64 ± 3.19, $p = 0.001$). And no statistical significance was observed in the comparison of various pressures at different times between CCM and non-CCM patients ($p > 0.05$). At the end of follow-up, 5 (6.1%) patients died. LAVI($P = 0.049$, HR 1.169, 95%CI [1.001-1.365]), MELD score($P = 0.026$, HR = 3.082, 95% CI [1.142-8.319]) and preoperative RAP ($p = 0.044$, HR = 2.015, 95%CI [1.018-3.987])were significantly associated with the mortality. **Conclusion:** In conclusion, cirrhotic patients with HBV infection as the primary etiology exhibit an effective regulatory capacity in response to hemodynamic alterations elicited by TIPS within short-term, irrespective of CCM presence. A longer and comprehensive evaluation are needed to find out the impact on outcomes in the future studies.



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Jennifer Linge – AMRA Medical AB: Employee, Yes, No; Eli Lilly: Consultant, No, No; BioMarin: Speaking and Teaching, No, Yes;
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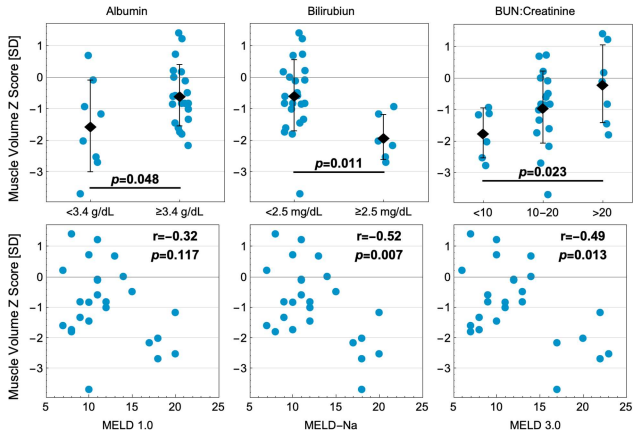
3090-A | MUSCLE VOLUME Z-SCORE IS LOWER IN HIGH-RISK PATIENTS AWAITING LT – INTERIM RESULTS FROM A LIVER TRANSPLANT WAITLIST NATURAL HISTORY STUDY

Mikael Fredrik Forsgren[1,2], Seung Lee[3], Jennifer Linge[1,2], Danielle Kirkman[4], Vaishali Patel[3], Per Widholm[2], Geneva Roche[4], Hiba Kamal[4], Olof Dahlqvist Leinhard[1,2] and Mohammad S. Siddiqui[4], (1) Linköping University, (2)Amra Medical AB, (3)Virginia Commonwealth University Health System, (4)Virginia Commonwealth University

Background: There is an unmet need for accurate and robust biomarkers identifying patients with liver cirrhosis at risk of adverse clinical events while waiting for liver transplantation (LT). Such biomarkers may also support the development of therapeutic options. A magnetic resonance imaging (MRI) based assessment (Muscle Assessment Score [MAsS]) combining muscle fat infiltration and muscle volume z-score (MVZ), has been developed to describe muscle health. Large population studies have shown that MAsS predicts physical function and hospitalization. Importantly, MVZ has been shown to be independent to sex and BMI. There is no data on evaluation of MVZ in patients awaiting LT. The aim was to assess the relationship between MVZ and L3 skeletal muscle index (L3-SMI) to blood samples and MELD in a prospective longitudinal study of patients with liver cirrhosis who are awaiting LT. **Methods:** MAsS and L3-SMI was measured using AMRA® Researcher based on an 8 min MRI acquired within the same week as blood samples (bilirubin, albumin, glomerular filtration rate [eGFRcr], blood urea nitrogen to creatinine ratio [BUN:Cr]). MELD scores (1.0, Na, 3.0) were calculated. T-test and Pearson correlation were used for statistical testing. **Results:** The first 31 patients (10 males, BMI 29.3 ± 6.6 kg/m^2, age 55 ± 11 yrs, with NASH cirrhosis or alcoholic-related cirrhosis) with complete MRI and blood samples at baseline were included. There was no difference in MVZ nor L3-SMI between NASH (n = 20) and alcoholic-related cirrhosis. Patients with low albumin had lower MVZ (-1.53 v -0.57 SD, p = 0.048) as did those with high total bilirubin (-1.89 v -0.56 SD, p = 0.011). There was no difference for eGFRcr. Patients with high blood urea had smaller muscles than those with low (-1.73 v -0.17 SD, p = 0.023) – within those groups there were no difference in kidney function (eGFRcr). L3-SMI was lower for patients with low compared to high blood urea (40.7 v 48.6 cm^2/m^2, p = 0.043), no other blood test where significant for L3-SMI. MVZ was strongly correlated with MELD-Na and 3.0. L3-SMI was not correlated to any MELD score (Fig). **Conclusion:** In patients with liver cirrhosis awaiting LT, MVZ was low for abnormal albumin, bilirubin, and blood urea. Those patients had between 1-1.5 SDs smaller muscles than expected compared to those presenting within normal levels. In addition, MVZ had a strong negative correlation with modern MELD scores. The same associations were only found for L3-SMI within blood urea, indicating that MVZ has a stronger link to poorer patient condition. Since body composition z-scores are independent to BMI and sex it may be translated in to the clinic much easier than volumetric measurements. Thus, z-scores may have the potential to supplement the diagnostic performance of the MELD score to predict clinical events and therefore improve clinical care for patients awaiting transplant, this requires further validation in well designed prospective studies.



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3091-A | NEUROFILAMENT LIGHT CHAIN AS POTENTIAL BIOMARKER FOR OVERT HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS

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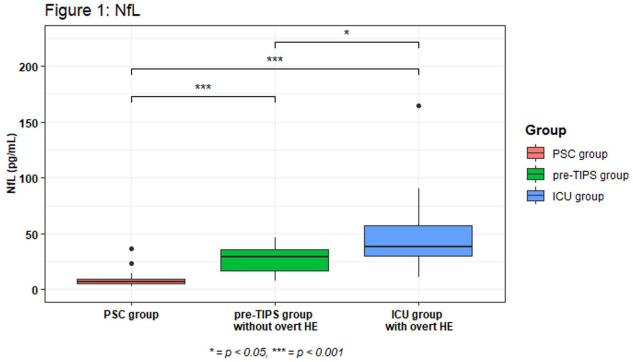
Background: Hepatic encephalopathy (HE) is one of the most frequent complications of cirrhosis. Hyperammonemia plays a key-role in its pathogenesis and is currently the only biomarker in blood supporting the clinical diagnosis. However, ammonia is less suitable for monitoring and predicting HE severity and outcome. Several studies showed that HE causes irreversible damage to the brain. Cerebral damage may induce a release of neuronal proteins like neurofilament light chain protein (NfL) and glial fibrillary acidic protein (GFAP) in body fluids including blood plasma. We hypothesized that neuronal proteins could be potential blood biomarkers for HE. **Methods:** Patients' plasma samples from three prospective cohorts were analyzed using single molecule assay (Simoa). Included patients had different stages of liver disease and HE severity and were matched based on age and sex using propensity matching. The first cohort consisted of 34 patients with primary sclerosing cholangitis (PSC) with compensated disease without overt HE (68 % male, 55 y (± 14)) and functioned as negative disease control group. The second cohort consisted of 17 patients with advanced liver disease without overt HE before elective transjugular intrahepatic portosystemic shunt (TIPS) placement (65 % male, 61 y (± 10)). The third cohort consisted of 17 patients with decompensated cirrhosis admitted to the ICU for stage IV overt HE (53 % male, 58 y (± 11)). **Results:** A total of 68 samples were analyzed. Median NfL concentrations were for the PSC group: 7.3 pg/ml [5.6 - 9.6 pg/ml], the pre-TIPS group 29.3 pg/ml [16.6 - 35.8 pg/ml] and the ICU group 38.6 pg/ml [30.1 - 57.0 pg/ml]. Concentrations in the pre-TIPS group and ICU group were both higher compared to the PSC group (both $p < 0.001$) and concentrations in the ICU group were also higher compared to the pre-TIPS group ($p = 0.03$) (Figure 1). Median GFAP concentrations were 83.8 pg/ml [66.9 - 106.6 pg/ml], 125.8 pg/ml [88.5 - 166.8 pg/ml] and 138.7 pg/ml [100.9 - 178.2 pg/ml] for the PSC group, pre-TIPS group and ICU group, respectively. Concentrations in the pre-TIPS group and ICU group were higher compared to the PSC group ($p < 0.001$ and $p = 0.02$) while there was no observed difference between the ICU and pre-TIPS group. Plasma NfL and GFAP concentrations correlated with Model for End-Stage Liver Disease (MELD) scores ($R = 0.58$ and $R = 0.40$, *$p < 0.001$, each*). **Conclusion:** Plasma NfL deserves further evaluation as a potential biomarker for oHE and strongly correlates with the MELD score in our limited cohort.

Figure 1: NfL



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3092-A | NEUTROPHIL-TO-LYMPHOCYTE RATIO PREDICTS SHORT- AND LONG- TERM READMISSION OF PATIENTS WITH HEPATIC ENCEPHALOPATHY

Rui Huang and Lin Zhang, Peking University People's Hospital

Background: Hepatic encephalopathy (HE) is an important complication of end-stage of liver disease, portending poorer outcomes. The readmission rate of patients with cirrhosis was 20-30% in 30 and 90 days, and the most common reason was HE. Several factors were reported as predictors of readmission in HE patients. However, long-term studies are lacking and few new serological indicators beyond liver parameters have been found. Aiming to explore simple and effective predictors of short- and long-term readmission of HE patients, we performed this retrospective study. **Methods:** We performed a single-center retrospective study of adult patients who were admitted with HE. The primary endpoint was the first liver-related readmission in 30, 90 and 180 days. Logistic regression analysis and multiple linear regression analysis were performed to describe predictors associated with readmission and length of the first hospitalization. **Results:** 424 patients, who were admitted with HE, were included. 24 (5.7%), 63 (14.8%) and 92 (21.7%) patients were

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underestimates the rate, LOS, and costs of OHE hospitalizations.

Table 1. Hospitalization characteristics

	OHE hospitalization Definition 1[4]	OHE hospitalization Definition 2[5]
Number of hospitalizations	**33,127**	**99,217**
Billing charge[1], mean ± SD [median]	56,648 ± 101,999 [33,043]	139,870 ± 238,751 [72,686]
Length of stay, mean ± SD [median]	5.2 ± 6.2 [4]	10.4 ± 12.3 [7]
OHE-related medications		
Rifaximin 550mg, n (%)	20,516 (61.9%)	54,849 (55.3%)
Days from admission to first dose, mean ± SD [median]	0.7 ± 1.8 [0]	2.6 ± 5.9 [1]
Lactulose, n (%)	30,428 (91.9%)	95,598 (96.4%)
Days from admission to first dose, mean ± SD [median]	0.2 ± 1.2 [0]	1.9 ± 4.8 [1]
Diagnosis[2], n (%)		
OHE[3]	33,127 (100.0%)	36,613 (36.9%)
Cirrhosis	26,979 (81.4%)	79,866 (80.5%)
Altered mental status	12,636 (38.1%)	29,148 (29.4%)
Ascites	12,251 (37.0%)	40,425 (40.7%)
Portal hypertension	8,740 (26.4%)	26,550 (26.8%)
Unspecified encephalopathy	5,864 (17.7%)	79,521 (80.1%)
Varices	5,719 (17.3%)	16,433 (16.6%)
Hepatorenal syndrome	2,124 (6.4%)	8,813 (8.9%)
Spontaneous bacterial peritonitis	696 (2.1%)	4,420 (4.5%)

OHE: overt hepatic encephalopathy; SD: standard deviation

[1]Billing charge was defined as the total charge amount of billed items during the hospital encounter.

[2]OHE (as defined by CMS GEMS K72.01, K72.11, K72.90, K72.91, K70.41, K71.11), cirrhosis (K70.3, K71.7, K74.6, K74.3, K74.4, K74.5), altered mental status (R41.82), ascites (K70.11, K70.31, K71.51, R18), portal hypertension (K76.6), unspecified encephalopathy (G93.40, G93.41, G93.49), varices (I85, I86.4), hepatorenal syndrome (K76.7, K91.83), and spontaneous bacterial peritonitis (K65.2) were defined using International Classification of Diseases, Tenth Edition codes.

[3]Among hospitalizations defined using definition 1, OHE codes must be coded as the primary diagnosis only.

[4]Definition 1 includes hospitalizations with OHE as a primary diagnosis.

[5]Definition 2 includes hospitalizations with in-hospital rifaximin/lactulose use combined with a diagnosis for altered mental status, unspecified encephalopathy, or cirrhosis.

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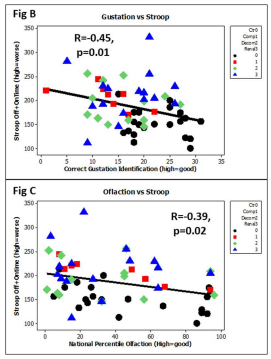
3109-A | TASTE AND SMELL CHANGES AFFECT EATING-RELATED QUALITY OF LIFE AND ARE LINKED WITH COGNITIVE IMPAIRMENT IN CIRRHOSIS AND RENAL FAILURE PATIENTS

Andrew Fagan[1], Courtney Brown[2], Mary Leslie Gallagher[3], Travis Mousel[1], Michael Fuchs[4], Puneet Puri[5], Brian C. Davis[6], James Wade[5], Nilang Patel[1] and Jasmohan S. Bajaj[7], (1)Virginia Commonwealth University and Richmond VA Medical Center, (2) Richmond VAMC, (3)McGuire Veterans Affairs Medical Center, (4)Mcguire Veterans Affairs Medical Center, Moseley, VA, (5)Virginia Commonwealth University, (6) Hunter Holmes McGuire VA Medical Center, (7)Virginia Commonwealth University and Central Virginia Veterans Healthcare System, Richmond, VA

Background: Cirrhosis is linked with poor nutrition, which could partly be due to anorexia in hepatic encephalopathy (HE) & coexistent renal failure. Taste & smell perception affect appetite but their role in cirrhosis ± dialysis are unclear. Aim: Define impact of cognitive impairment in cirrhosis ± dialysis on taste & smell perception & study their impact on eating-related QOL. **Methods**: Healthy people & outpts with cirrhosis (± decompensation), on dialysis underwent taste & smell tests, cognitive testing using (PHES, high = better, Stroop, high = worse), SAS questionnaire for olfactory impact on life (high = worse) and quality of life (QOL) testing using Sickness Impact Profile (SIP, high = worse), which also has an "eating" QOL component. Pts with past/current COVID-19, current/recent alcohol or tobacco use were excluded. Tastes studied were sweet, sour, salty, brothy & bitter. Smell was tested using the NIH toolbox. Taste & smell results were compared between groups & correlated with cognition. Multi-variable analysis for taste/smell & eating portion of SIP was performed. **Results**: 59 subjects (22 healthy, 21 cirrhosis & 16 dialysis), predominantly men, were included (fig A). Of the cirrhosis pts, 8 were compensated, 13 decompensated (11 HE; all lactulose/8 rifaximin, MELD 11). Diabetes was similar across diseased pts. Taste & smell test: Controls had the best taste discrimination while cirrhosis & dialysis pts were similarly impaired; no impact of HE was seen. Sweet & sour tastes were most affected. While smell detection was not different, diseased groups had worse SAS results (FigA). Correct taste and smell were linked ($r = 0.5, p < 0.001$). Diabetes did not affect taste/smell.
Cognitive tests & QOL: Eating-related and overall QOL was worst in advanced pts (Fig B). Stroop & PHES impairment were also worse in diseased pts vs controls. Taste was significantly correlated with PHES ($r = 0.4$, $p = 0.02$) and Stroop regardless of HE or dialysis (Fig B). Smell perception percentile was only correlated with Stroop (Fig C).
Multivariable analysis: for *taste*, high (or good) PHES (T value 2.5, $p = 0.01$) & smell results (2.2, $p = 0.03$) were contributory, while for *smell*, taste correct results (T value 2.6, $p = 0.02$), low (= good) Stroop (-0.32, $p = 0.008$) & age (2.2, $p = 0.03$) were linked. Eating impairment on SIP was linked with high (= worse) Stroop (T value 2.2, $p = 0.03$) & high (= worse) SAS smell QOL questionnaire (2.8, $p = 0.008$). **Conclusion**: Taste perception and smell-related quality of life in cirrhosis is significantly impaired compared to controls and is similar to dialysis pts. Smell-related QOL & advanced disease affected eating behavior. Cognitive impairment, especially on Stroop, rather than simple HE/decompensation was linked with taste and smell. Altered taste and smell perception should be considered as a contributor towards poor nutrition, eating and QOL in patients with cirrhosis and renal failure, especially those with cognitive impairment.

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

Fig A	Healthy (n=22)	Comp cirrhosis (n=8)	Decomp Cirrhosis (n=13)	On Dialysis (n=16)	P value (all groups)
Age	55.0±9.9	69.6±5.1	66.1±6.3	62.9±12.6	0.001
Male Gender	18	8	13	15	0.91
Diabetes	0	5	10	11	<0.001
Cognition					
PHES (↑=good)	-0.10±1.9	-4.25±2.38	-2.39±2.60	-5.06±3.8	<0.0001
Stroop time (↑=poor)	155.2±27.21	201.7±29.9	204.2±36.2	212.1±53.1	<0.0001
Taste (↑=good)					
Total correct	26.3±6.9	16.0±5.4	19.7±6.9	20.0±7.8	0.002
Sweet correct	5.4±2.4	2.6±3.5	3.5±2.2	2.9±2.3	0.004
Sour correct	6.6±1.0	4.5±2.5	5.0±2.1	5.4±1.9	0.01
Salty correct	5.8±2.1	3.8±2.5	4.3±2.4	5.1±2.3	0.10
Brothy correct	4.3±2.9	2.4±1.8	3.4±2.3	3.0±2.3	0.18
Bitter correct	4.5±2.4	2.8±1.9	3.4±1.9	3.5±2.4	0.22
Smell (↑=good)					
National percentile (↑=good)	46.1±31.7	40.0±31.7	37.1±32.3	30.1±26.6	0.52
PROs					
SAS: Smell QOL questionnaire (↑=worse)	3.2±6.6	2.9±3.1	6.9±6.7	12.1±13.0	0.02
SIP (↑=worse)					
Total SIP	9.2±10.5	7.9±10.7	19.5±15.0	20.4±17.7	0.02
Eating SIP	2.6±3.8	2.1±4.2	9.3±8.6	10.2±7.9	0.001



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3110-A | THE ASSOCIATION BETWEEN ANGIOTENSIN CONVERTING ENZYME INHIBITOR OR ANGIOTENSIN RECEPTOR BLOCKER EXPOSURE AND PROGRESSION OF CIRRHOSIS

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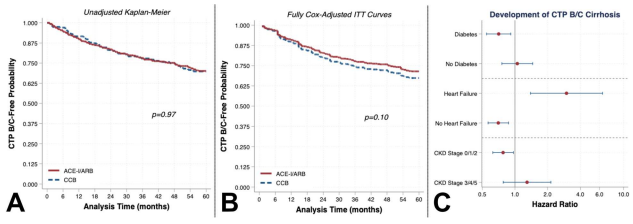
Background: Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) may reduce fibrosis, portal hypertension, and hepatic decompensations in patients with chronic liver disease or compensated cirrhosis. However, the clinical benefits and role of ACEi/ARB in cirrhosis remains unclear. To characterize this, we evaluated the association between ACEi/ARB and progression of cirrhosis in a national cohort. **Methods:** Using the Veterans Health Administration, we performed a retrospective, active comparator new user study of patients with Child-Turcotte-Pugh (CTP) Class A cirrhosis newly initiated on ACEi/ARB or calcium channel blockers (CCB, comparator). Kaplan-Meier analysis was used to evaluate unadjusted associations between medication exposure and incident development of CTP Class B/C cirrhosis. Inverse probability treatment weighting (IPTW) was used to balance key confounders in Cox regression analyses. Subgroup analyses characterized the impact of diabetes, heart failure, and chronic kidney disease on the association between ACEi/ARB exposure and development of CTP Class B/C Cirrhosis. **Results:** The cohort included 588 ACEi/ARB and 249 CCB new initiators. ACEi/ARB users were more likely to have a higher BMI (29.6 vs 27.5 $p < 0.001$), have lower stages of CKD, and more metabolic comorbidities including diabetes, coronary artery disease, and heart failure with reduced ejection fraction. In unadjusted Kaplan-Meier analysis, ACEi/ARB exposure was not associated with incident development of CTP Class B/C cirrhosis ($p = 0.97$, Figure A). Similarly, in fully adjusted IPTW Cox regression, ACEi/ARB exposure was not associated with development of CTP Class B/C cirrhosis (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.70-1.03, $p = 0.10$, Figure B). In subgroup analyses, ACEi/ARB exposure was associated with reductions in development of CTP Class B/C cirrhosis in patients with diabetes, without heart failure, and with early stage CKD (Stage 0-2) and associated with increased development of CTP Class B/C in patients with heart failure (Figure C). **Conclusion:** In patients with CTP A cirrhosis overall, ACEi/ARB exposure was not associated with development of CTP Class B/C disease, however we did identify relevant subgroups where the risk was either increased or decreased. Future research should better characterize cirrhosis patient subgroups that may benefit from ACEi/ARB exposure and elucidate underlying mechanisms.



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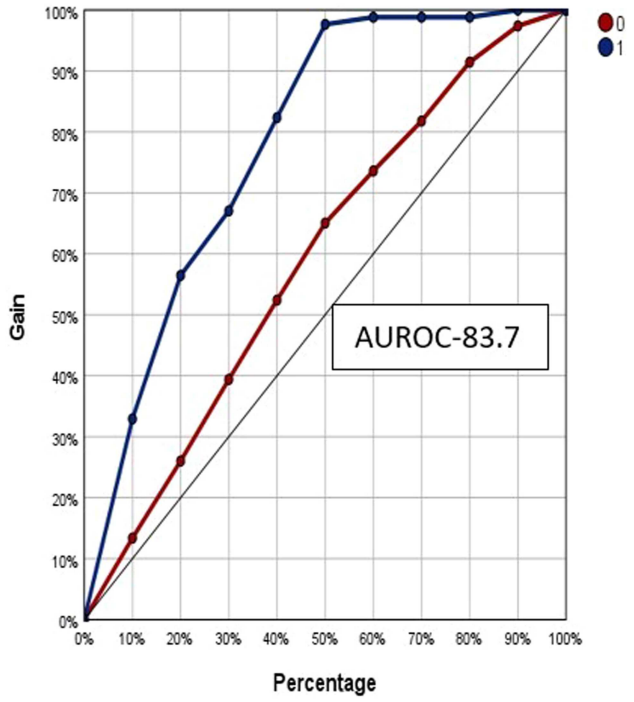
Background: Patients with decompensated cirrhosis are associated with various complications alongwith increased inpatient mortality.However data regarding appropriate triaging of these patients is lacking.The study was aimed to identify risk factors and develop a machine learning model to predict mortality in cirrhotic patients presenting to the ER **Methods:** Cirrhotic Patients presenting to emergency room were prospectively enrolled between February 2023 to April 2023 . Baseline data at admission including demographics, laboratoty values were included.AI-modelling was done after appropriate mining, feature engineering, splitted randomly into train and test sets (70:30).The objective of the study was to identify risk factors in the ER for prediction of mortality in patients with liver cirrhosis **Results:** A total of 355 patients were included for the analysis; males(62.1%),MELD score 19 ± 3.6,predominant etiology ethanol(47.9%) and NASH(26.7%), overall mortality seen in 91(20.7%)patients. Triaging to ward/ high dependency unit(HDU)/ intensive care unit(ICU) was seen in 164(46.6%)/100(28.3%)/73 (20.7%) patients respectively with in -hospital ICU transfers(IH-ICU) in 39(11%)patients. Predominant patient complaints at ER included altered sensorium(n = 82(23.2%), bleeding(n = 71(20.1%), breathlessness requiring oxygen supplementation(n = 49(13.8%).Sepsis at admission alongwith (n = 43/12.1%) heamodynamic shock were significant (n = 42/11.9%) ($P < 0.01$).Nosocomial sepsis was seen in 18(5.1%) with overall SIRS at admission in 155(46.1%) patients.Mean arterial lactate was 2.6 ± 2.1mmol/L with presence of Acute Kidney Injury(AKI) in 56(15.9%)patients.Carbapenem use was reported in 121(34.1%) with antibiotic escalation in 161 (45.5%) patients($p < 0.01$).Door to antibiotic time /door to fluid time was 9.5 ± 4.4 mins/13.7 ± 7.3 mins ($p < 0.01$) respectively.On multivariate analysis NASH (O.R-3.3 95%C.I-1.41-7.42),history of ascitic tap(O.R-2.2 95% C.I-1.06-4.05),history of pneumonia(O.R-7.2 95% C.I-1.2-41.8),duration of hospital stay > 5 days(O.R-7.6 95% C.I-4.1-14.2), ICU admission(O.R-6.1 95% C.I-3.0-12.2) were found to be significant($p < 0.01$) factors for mortality. The REACH-ER model was formulated with AUROC-83.7 ($p < 0.01$), and a score > 28 predicted in-hospital mortality. Using neural networks the overall accuracy of the model was 89.96% with NPV 94% and specificity 95 %.The training cohort had an accuracy of 86% while testing cohort had an accuracy of 74%. The independent variables of importance included duration of hospital stay > 5days (100%)/ICU(96.6%)/NASH(88.2%)/Ascitic tap(48.5%)/ pneumonia(16.8%) **Conclusion:** The REACH-ER ML model can reliably predict mortality in cirrhotic patients presenting to the ER. Simple ML algorithms besides clinical syndromic presentation could help in treatment decisions, prognostications, and escalation of care including early transplant work-up



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3117-A | VALIDATION AND CUTOFF TIME OF THAI ENCEPHALAPP STROOP TEST FOR DIAGNOSIS OF COVERT HEPATIC ENCEPHALOPATHY

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Background: The EncephalApp Stroop Test was developed to diagnose covert hepatic encephalopathy (CHE). However, information regarding the best cut-off (Ontime+OFFtime) is still scant in outside North America populations. We aim to analyze the usefulness of this diagnostic method and to describe a cut-off value of the Thai version EncephalApp (Thai EncephalApp) stroop test to screen CHE in Thailand. **Methods:** In this cross-sectional and single-center study, median and 95% higher from the expected Stroop value for every healthy controls defined the

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diagnosis of CHE. We evaluated gender, age, education, etiology of cirrhosis, Child-Pugh/MELD scores, and previous hepatic encephalopathy (HE). Healthy controls and patients without HE were compared for the task validation. The Chi-square and Mann-Whitney tests, and logistic regression analysis were used for statistical evaluation. **Results:** We included 171 patients with cirrhosis (79% male) and 144 controls (46% male) around 51y. Viral hepatitis (47%) was the major etiology of cirrhosis. The median MELD was 10 and Child-Pugh A was more frequent (84%). There was no significant difference in test results between controls and patients without HE. The regression formula in healthy people was made using age, gender, and education, of which only age and education were significant which a cut-off of > 175 sec defined the diagnosis of CHE (OffplusOn = 121 + 1.35 Age[year] – 1.77 Study[year]) which found 39% of CHE. Patients with CHE on Thai EncephalApp Stroop Test was additive to MELD score with p = 0.06 on multivariate analysis. **Conclusion:** Thai EncephalApp Stroop Test may be useful in a stepwise diagnosis algorithm or even as a stand-alone screening tool to detect CHE in Thai patients with cirrhosis.

Table 1: Data comparing hospitalized patients and healthy volunteer participants

	Cirrhosis (n = 171)	Healthy volunteers (n = 144)	*p*-value
Age (y)	57 ± 9	49 ± 10	<0.001
Education (y)	14 ± 4	15 ± 4	0.001
Sex (men/women)	135/36	66/78	<0.001
MELD score	10 ± 4	-	
CTP score, % (A/B/C)	84.3/13.3/2.4	-	
Etiology, %	27.7/20.5/21.1/6	-	
(HBV/HCV/Alc/others)		-	
Prior OHE, %	29.9	-	
HistoryDecompensated,%	29.9	-	
on Lactulose,%	19.3	-	
Standard tests	59.44 ± 34.29	41.76 ± 18.81	<0.001
NCT-A	181.18 ± 197.90	80.90 ± 73.77	<0.001
SDT	102.30 ± 119.79	48.11 ± 34.95	<0.001
LTT	1.44 ± 10.13	0.63 ± 1.59	0.342
Thai EncephalApp			
OffTime	97.40 ± 25.72	73.85 ± 10.18	<0.001
OnTime	113.51 ± 34.76	87.24 ± 18.63	<0.001
Off+OnTime	209.01 ± 58.33	160.65 ± 27.80	<0.001
Off-OnTime	16.12 ± 18.29	14.07 ± 12.16	0.255
No. of runs for Off state	5.77 ± 1.40	5.56 ± 0.95	0.120
No. of runs for On state	6.05 ± 1.86	5.78 ± 1.08	0.117

Disclosures: The following people have nothing to disclose: Apiwat Augkaros, Atchara Sereepaiboonsub, Theeranun Sanpajit, Jasmohan S. Bajaj, Sakkarin Chirapongsathorn

3118-A | VALIDATION AND IMPACT OF RECOMPENSATION USING BAVENO VII CRITERIA AFTER SUSTAINED VIRAL RESPONSE AMONG PATIENTS WITH HEPATITIS C-RELATED DECOMPENSATED CIRRHOSIS TREATED WITH DIRECT ACTING ANTIVIRALS

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Background: Chronic hepatitis C virus (HCV) infection is a leading cause of chronic liver disease (CLD) worldwide. Its prevalence is of particular significance in developing countries. Generalized access to Direct Acting Antivirals (DAA) in public healthcare has greatly increased the rates of sustained virological response (SVR), but evidence that correlates it with clinically significant improvement is lacking. The Baveno VII consensus has recently proposed the term of cirrhosis recompensation as objective evidence of clinical improvement. In the present study, we aimed to validate this new definition in patients with HCV-related cirrhosis treated with DAA after SVR. **Methods:** This is a single center, prospective cohort study, which included all patients with decompensated ACLD (dACLD) due to HCV, older than 18 years, that had received DAA and achieved SVR, at our institution in Mexicali, Mexico, from January 1, 2018, to October 31, 2021. Baseline patient characteristics were collected, participants were followed up for clinical events, biochemical tests, and VCTE at the time of SVR, 12 weeks and 52 weeks after achieving virological cure, the primary endpoint was cirrhosis recompensation rate according to BVII definition, direct comparison of variables and outcomes was established between those who reached the PO. Secondary outcomes were improvement in CTP, MELD-Na, LS by VCTE, and absolute platelet count. Multivariate regression was used to identify predictors of recompensation. Patients with an additional etiology of CLD, severe

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

The following people have nothing to disclose: Efe Ozkaya, Octavia Bane, Amine Geahchan, Aaron Fischman, Swan N. Thung

3130-A | PHARMACOKINETICS AND SAFETY OF BELAPECTIN, A CANDIDATE DRUG FOR NASH CIRRHOSIS, IN SUBJECTS WITH NORMAL HEPATIC FUNCTION AND SUBJECTS WITH VARYING DEGREES OF HEPATIC IMPAIRMENT

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Background: Belapectin is a large polysaccharide carbohydrate molecule that inhibits the glycoprotein galectin-3. Belapectin is currently under evaluation in a Phase 2b/3 trial as a monotherapy for the prevention of esophageal varices in patients with NASH cirrhosis and portal hypertension. A Phase 1, open-label, non-randomized, parallel-group study was conducted to determine the effect of hepatic impairment on the pharmacokinetics (PK), safety, and tolerability of a single IV infusion of belapectin at 4 mg/kg Lean Body Mass (LBM) compared to matched healthy subjects with normal hepatic function (NCT04332432). **Methods:** Subjects were enrolled based on their hepatic function, as determined according to the Child-Pugh score: Mild (Child A), Moderate (Child B), and Severe (Child C). Healthy subjects with normal hepatic function were demographically matched by age (± 10 y), sex, and body mass index (BMI ± 20%) to subjects with hepatic impairment. Plasma concentrations of belapectin were determined with a validated bioanalytical assay at pre-infusion, 3, 24, 36, 48, 72, 120, 210, and 336-hours post-infusion. Safety evaluation included adverse events, ECGs, biochemistry, and hematology. **Results:** The study enrolled and dosed 38 subjects (8 mild, 8 moderate, 8 severe, 14 healthy). All subjects received a single dose of belapectin at 4 mg/kg LBM. Belapectin was well tolerated and appeared safe. There were no treatment emergent SAEs; all adverse events reported were mild, except for one subject who experienced nausea and vomiting of moderate severity. There were no ECG findings, and no subject discontinued prematurely from the study. A summary of geometric means (CV%) of key PK parameters of belapectin is in the Table. **Conclusion:** Belapectin at 4 mg/kg LBM, the highest dose evaluated in the ongoing Phase 2b/3 study, appeared safe and was well tolerated. Hepatic function had minimal impact on key PK parameters of belapectin suggesting that no dose adjustment of belapectin will be required for patients with increasing severity of hepatic impairment.

TABLE: Geometric Means (CV%) of Key Pharmacokinetic Parameters of Belapectin in Subjects with Normal Hepatic Function and Subjects with Varying Degrees of Hepatic Impairment

PK Parameter	Hepatic Function			
	Normal (n=14)	Mild (n=8)	Moderate (n=8)	Severe (n=8)
C_{max} (µg/mL)	42.6 (20.2)	41.3 (16.2)	38.3 (25.4)	37.2 (12.5)
$AUC_{0\text{-}t}$ (µg·hr/mL)	2,360 (24.3)	2,440 (28.0)	2,410 (25.2)	2,210 (22.2)
$AUC_{0\text{-}inf}$ (µg·hr/mL)	2,400 (26.6)	2,500 (26.6)	2,500 (26.0)	2,300 (21.7)

Disclosures: Ezra Lowe – Galectin Therapeutics: Employee, Yes, No;
Eric Lawitz – Abbvie, Gilead Sciences, Intercept: Speaking and Teaching, No, No; Akero, Boehringer Ingelheim, BMS, Intercept, Novo Nordisk, Metacrine, Sagimet, Terns: Advisor, No, No; 89Bio Inc., AbbVie, Akero Therapeutics, Allergan, Alnylam Pharmaceuticals Inc., Amgen, Ascelia Pharma, AstraZeneca, Axcella Health, Boehringer Ingelheim, Bristol-Myers Squibb, Conatus Pharmaceuticals, Cymabay Therapeutics, CytoDyn, DSM, Durect Corporation: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
Stephen A Harrison – Novo Nordisk: Speaking and Teaching, Yes, No;
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♦ 3131-A | SINGLE NUCLEAR RNA SEQUENCING OF TERMINAL ILEUM IN PATIENTS WITH CIRRHOSIS DEMONSTRATES MULTI-FACETED ALTERATIONS IN THE INTESTINAL BARRIER

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Background: Cirrhosis & hepatic encephalopathy (HE) is associated with systemic inflammation and intestinal barrier dysfunction. However, the expression of inflammatory, defensin and mucus-producing genes at single cell level in the small intestine of patients with varying stages of cirrhosis is unclear. Aim was to determine differences in the key gene expression related to the production of mucus, defensins & inflammatory mediators in cirrhosis vs controls. **Methods**: Prepped colonoscopy was performed with pinch biopsies of the terminal ileum (TI) in controls, compensated (comp) & early decompensated (decomp);

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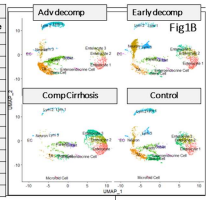
early (on lactulose) & advanced (on rifaximin). snRNA-seq was performed and Seurat 4.0, an R package was employed to analyse the feature-barcode matrices. Cell-type-specific marker genes were used for the identification of cell types. QIAGEN Ingenuity Pathway Analysis (IPA) was used to identify the cell-type specific pathways dysregulated in cirrhosis. Specific genes related to inflammation (IL-1, IL-6, TNFa) and mucus production were compared across all cell types and within enterocytes, goblet, and Paneth cells. **Results**: Subjects: We performed snRNA-seq in 4 subjects who were age-matched (56 y); the highest MELD was in the advanced decomp group (14) vs early decomp (9) vs comp (6). SnRNAseq successfully identified all different cell types. There is a significant loss of stem cells in all cirrhosis pts (1.55-5.74% vs 21.5% controls). The relative proportion of Paneth cells was higher in advanced decomp (18% vs 4-8% in the rest).
Inflammatory genes: IL1, IL6 and TNF-related genes were significantly upregulated in the enterocytes in all decompensated subjects, especially those with advanced HE compared to healthy control (Fig 1C).
Paneth cells: The greatest expression of defensin-coding genes was in controls, compensated cirrhosis vs decomp pts (advanced or not).
Goblet cells: Lower expression of goblet cell markers (FcGBP,CLCA1, and SPDEF, involved in differentiation of goblet cells, improving mucus regeneration and suppressing inflammation) was seen in advanced decomp pts. However, MUC2 expression, involved in mucin production was higher in both decomp groups. IPA: We found higher IL6, IFN gamma and alpha activation, adhesion, cytotoxicity, and migration of polymorphs and lymphocytes and lower xenobiotics handling (PXR, RXR) and protein kinase signaling in advanced decomp vs remaining groups. **Conclusion**: Using snRNA-seq in the terminal ileum of patients with compensated and decompensated cirrhosis compared to controls, we found a higher inflammatory expression along with suppressed defensin and mucus stabilization gene expression in decompensated compared to other groups. All cirrhosis pts had lower stem cell population versus controls. These alterations may contribute to the many aspects of intestinal barrier dysfunction in advanced cirrhosis.

Figure 1A	Advanced Decomp		Early Decomp		Comp Cirrhosis		Control	
	Count	Percentage	Count	Percentage	Count	Percentage	Count	Percentage
Endothelial Cell	61	2.01%	27	0.88%	5	0.20%	34	1.25%
Enterocyte 1	339	11.18%	473	15.44%	579	22.77%	294	10.84%
Enterocyte 2	123	4.06%	245	8.00%	464	18.25%	306	11.29%
Enterocyte 3	5	0.16%	156	5.09%	679	26.70%	78	2.88%
Enteroendocrine	47	1.55%	20	0.65%	26	1.02%	32	1.18%
Goblet Cell	53	1.75%	111	3.62%	174	6.84%	97	3.58%
Lym 1	422	13.92%	71	2.32%	38	1.49%	186	6.86%
Lym 2	326	10.75%	58	1.89%	58	2.28%	127	4.68%
Lym 3	26	0.86%	329	10.74%	51	2.01%	141	5.20%
Neuron	151	4.98%	1070	34.92%	20	0.79%	183	6.75%
Paneth Cell	557	18.37%	148	4.83%	214	8.42%	215	7.93%
Stem Cell	47	1.55%	155	5.06%	146	5.74%	584	21.54%
TA	848	27.97%	187	6.10%	61	2.40%	405	14.94%
Total	3032	100.00%	3064	100.00%	2543	100.00%	2711	100.00%



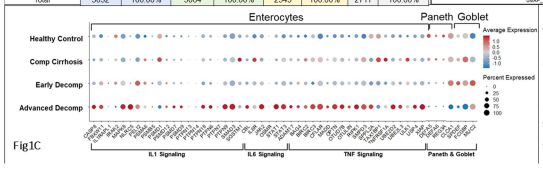


Fig1A: Cell types
Fig1B: UMAP analysis
Fig1C: Gene Expression across cell types and groups

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The following people have nothing to disclose: Xixian Jiang, Andrew Fagan, Bhaumik Patel
Huiping Zhou:

3132-A | A NONINVASIVE MODEL TO PREDICT CLINICALLY SIGNIFICANT PORTAL HYPERTENSION IN PORTO-SINUSOIDAL VASCULAR DISEASE

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Background: Porto-sinusoidal vascular disease (PSVD), formerly referred to as idiopathic non-cirrhotic portal hypertension, encompasses a diverse group of disorders that primarily affects the porto-sinusoidal vascular system resulting in portal hypertension. Multiple etiologies including immunologic, hematologic, genetic disorders, infections, toxins, and drugs can cause PSVD. Variceal bleeding is the common initial manifestation of clinically significant portal hypertension (CSPH) in patients with PSVD. BAVENO VII criteria are a validated noninvasive model to identify CSPH and varices in cirrhotic patients. However, these criteria do not apply to PSVD. We aimed to develop a noninvasive diagnostic model for predicting varices and CSPH in PSVD. **Methods:** We included a single center cohort of biopsy proven PSVD patients who were part of a prospective natural history protocol (NCT02417740). All patients had liver stiffness (LSM) measured using transient elastography and upper endoscopy or imaging studies assessing for presence of CSPH. CSPH was defined by BAVENO VII specific criteria as the

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3207-A | DISTINCT EFFECTS OF SENESCENCE CLEARANCE ON ALCOHOL-INDUCED LIVER INJURY IN YOUNG AND AGING INK-ATTAC MICE

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Background: Senescence is a state of permanent cell cycle arrest employed by cells due to replicative or stress-related mechanisms. The INK-ATTAC is a genetic tool based on dimerization of active caspase 8 domain by the AP20187 compound for inducible elimination of senescent cells under the control of p16Ink4a promoter. This study aims to use INK-ATTAC transgenic mice and examine roles of senescence during alcohol-induced liver injury in young and aging conditions. **Methods:** Suicide gene-meditated ablation of p16Ink4a-expressing senescent cells was carried out through intraperitoneal injection of AP20187 into young (8-week-old) or aging(20-month-old) INK-ATTAC mice at or age respectively. The chronic-on-acute liver injury was induced by feeding of 5% ethanol-containing Lieber DeCarli diet for one month plus repetitive ethanol binge (5 g/kg body weight, once per week for total 4 times). AP20187 (10 mg/kg) was administered to the young or aging adult mice every 3 days before the end time points. Control mice received the same treatment except vehicle for the alcohol-induced liver injury. Hepatic inflammation, steatosis, and levels of serum markers for liver function were examined. **Results:** Higher levels of p16Ink4a and increased activities of senescence-associated beta-galactosidase were found in aging livers than those in young groups. Elimination of senescence in these old adult livers by AP20187 reduced number of neutrophils as revealed by IHC for myeloperoxidase (MPO), attenuated fat accumulation in Oil red staining, and decreased levels of alanine aminotransferase (ALT) and aspartate amino-transferase (AST) in sera compared to age-matched vehicle-treated controls, indicating that senescence clearance reduced ethanol-induced injury in aging livers. Further, elimination of $p16^{high}$ cells ameliorated immune cell infiltration. An enzyme-linked immuno-sorbent analysis showed that the higher cytokine secretion levels of IFN-γ, TNF-α and interleukin 6 (IL-6, a critical modulator of innate immunity) in the AP20187 treated group compared to age-matched vehicle-treated controls could be observed. **Conclusion:** Senescence clearance is beneficial and protects aging but not young mice from the ethanol-induced chronic-on-acute liver injury.

Disclosures: The following people have nothing to disclose: Tian Tian, Chunbao Sun, Sreenivasulu Basha, Hua Wang, Liya Pi

3208-A | EFFICACY AND SAFETY OF PLASMA EXCHANGE WITH HUMAN SERUM ALBUMIN 5% ON SHORT-TERM SURVIVAL IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE AT HIGH RISK OF HOSPITAL MORTALITY: APACHE STUDY DESIGN AND PROGRESS

Nikolaos T. Pyrsopoulos[1], Giovanni Perricone[2], Jasmohan S. Bajaj[3], Thierry Gustot[4], Thomas Reiberger[5], Mireia Torres[6], Peter Nelson[6], Javier Fernandez[7,8] and On behalf of the APACHE Study Investigators, (1)Rutgers-New Jersey Medical School, (2)Asst GOM Niguarda, (3)Virginia Commonwealth University, (4)HUB Erasme Hospital, Université Libre De Bruxelles, (5)Medical University of Vienna, (6) Grifols, (7)EF Clif, Easl-Clif Consortium and Grifols Chair, (8)Hospital Clínic, Idibaps and Ciberehd

Background: Acute-on-chronic liver failure (ACLF) is an increasingly recognized syndrome in patients with cirrhosis, characterized by acute decompensation of cirrhosis that results in severe organ injury with high rates of short-term mortality. Liver transplantation is currently the only treatment to improve survival. A pilot study suggested that plasma exchange with human serum albumin 5% (PE-A5%) as a replacement fluid is feasible and safe in patients with ACLF and may improve organ function and survival. The aim of this study is to assess PE-A5% as a treatment for patients with ACLF in a pivotal study **Methods:** A phase 3, multicenter, randomized (1:1), controlled, parallel-group, open-label study (APACHE) compares standard medical treatment (SMT) + PE-A5% (treatment arm) to SMT alone (control arm). PE-A5% is performed using Albutein 5% (Grifols). Treatment schedule consists of two initial PE-A5% sessions on consecutive days followed by every other day PE-A5% (minimum 4, maximum 9 PE-A5%). Patients receive IVIG (200 mg/kg) after every 2 PE-A5% to prevent hypogammaglobulinemia-associated infections, and FFP after each PE-A5% to prevent coagulopathy. Eligible patients are adult (18-79 years old), with ACLF-1b, ACLF-2, or ACLF-3a at admission or during hospitalization. Main exclusion criteria are patients with ACLF-1a or ACLF-3b, ACLF > 10 days prior to randomization, septic shock requiring norepinephrine (> 0.3 μg/kg/min) or a second vasopressor, active infection, and severe respiratory failure. **Results:** Target enrollment is 380 patients with ACLF at high risk of hospital mortality. As of May 2023, enrollment is occurring at 26 sites across North America and Europe, with 244 patients screened and 208 patients randomized (54.7% of sample size). The primary efficacy endpoint is the 90-day overall survival. Secondary efficacy endpoints include 90-day transplant-free survival and 28-day overall survival. Main exploratory endpoints include overall and transplant-free survival at days 28 and 90, in-patient hospital and ICU

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stay, incidence of organ failures and ACLF course. Safety analyses include adverse events, vital signs, physical assessments, and laboratory tests. **Conclusion:** APACHE should provide pivotal results on the efficacy and safety of PE-A5% as a potential treatment to improve survival in ACLF (NCT03702920, EudraCT: 2016-001787-10).

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3209-A | ENGINEERED MESENCHYMAL STEM CELL-DERIVED EXOSOMES PROMOTE MACROPHAGE EFFEROCYTOSIS VIA ADAM9/MERTK AXIS IN ACUTE-ON-CHRONIC LIVER FAILURE

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♦ 3303-A | ALPHA-1 ANTITRYPSIN PIMZ, PISS AND PISZ PHENOTYPES ARE ASSOCIATED WITH INCREASED LIVER RELATED DEATH IN ALCOHOL-ASSOCIATED AND NAFLD CIRRHOSIS

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Background: Cirrhosis related to alpha-1 antitrypsin deficiency (A1ATD) is rare, but likely under-diagnosed. Prior studies examining association of non-PiZZ phenotypes on liver disease outcomes, particularly cirrhosis, have been limited by sample size. We aimed to examine the association of non-PiZZ variants on outcomes of cirrhosis due to NAFLD and alcohol. **Methods:** This was a retrospective study of patients with cirrhosis from the Veterans Affairs Health System. Clinical and lab data on participants who underwent A1AT phenotype testing were identified, with A1AT phenotype extracted using natural language processing. A1AT was considered as a categorical variable-groups PiMM, PiMS, PiMZ, PiSS/SZ, and PiZZ. Participants with a diagnosis of NAFLD or alcohol-associated cirrhosis were included. Propensity score inverse probability of treatment weighting was performed to reduce confounding bias by creating a weighted sample that balanced the distribution of observed covariates between the various phenotypes. We excluded participants with decompensation at cirrhosis diagnosis for that outcome, but included them for outcomes of HCC and liver-related death (LRD). The associations between A1AT phenotype with decompensation, HCC, and LRD were modeled with Fine-Gray competing risks, with transplant and death as competing risks for decompensation/HCC, and transplant and non-LRD, competing risks for LRD. The multivariable models adjusted for age, race, sex, cirrhosis etiology, as well as time-varying BMI, platelet count, AUDIT-C and MELD. **Results:** Of 3189 participants with NAFLD/alcohol-associated cirrhosis who underwent A1ATD testing, the following phenotypes were identified: PiMM 2,628, PiMS 246, PiMZ 203, PiSS/SZ 61, and PiZZ 51 In participants with NAFLD cirrhosis, PiMZ phenotype was associated with an increase in LRD (subHazard Ratio [sHR] 4.77, 95% CI 3.50-6.50, $p < 0.001$), but not decompensation (sHR 1.15, 95% CI 0.99-1.33, $p = 0.06$) or HCC (sHR 0.83, 95% CI 0.59-1.15, $p = 0.25$), while PiSS/SZ phenotypes were associated with an increase in decompensation (sHR 1.57, 95% CI 1.35-1.81, $p < 0.001$), HCC (sHR 1.79, 95% CI 1.38-2.33, $p < 0.0001$), and LRD (sHR 8.14, 95% CI 6.02-11.01, $p < 0.0001$). In alcohol-associated cirrhosis, PiMZ phenotype was associated with an increase in decompensation (sHR 2.06, 95% CI 1.78-2.39, $p < 0.0001$), and LRD (sHR 1.65, 95% CI 1.22-2.24, $p = 0.001$), but not HCC (sHR 1.32, 95% CI 0.96-1.81, $p = 0.09$), while PiSS/SZ phenotypes were associated with an increase in LRD (sHR 4.81, 95% CI 3.62-6.39, $p < 0.0001$), but not decompensation (sHR 1.13, 95% CI 0.98-1.31, $p = 0.08$) or HCC (sHR not

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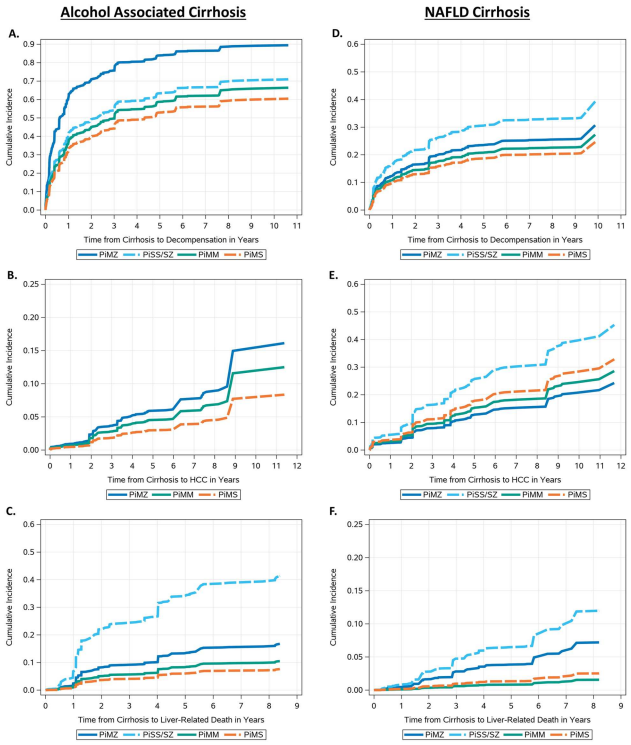
evaluable due to low event rate). **Conclusion:** In this large study of Veterans with NAFLD and alcohol-associated cirrhosis, A1ATD PiMZ, SS and SZ phenotypes are associated with increased liver-related complications. Testing for A1ATD phenotype in patients with cirrhosis is warranted to recognize those at higher risk of complications.



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◆ 3304-A | ALTERATIONS IN BILE ACID PHYSIOLOGY IN WILSON'S DISEASE

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Background: Wilson's disease (WD) is an autosomal recessive disorder that results in hepatic copper (Cu^{++}) accumulation due to mutations in the Cu^{++}-transporting P-type ATPase (ATP7B) transporter. WD is characterized by steatosis, fibrosis, cirrhosis, and liver failure. The composition of TCA cycle, amino acid, and glycolytic metabolites are changed in WD patients and *Atp7b*$^{-/-}$ mice. Previous studies revealed dysregulation of many FXR metabolic target genes, including Bsep, the major determinant for bile flow. We tested the hypothesis that the FXR-cistrome is decreased in *Atp7b*$^{-/-}$ mice and coincides with dysregulated bile acid homeostasis. **Methods**: RNA and ChIP-Seq analysis of livers was performed in 6-month-old *Atp7b*$^{-/-}$ and wild-type mice and significantly changed genes and FXR-binding events were overlapped. Bile acids were measured

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3442-A | IMPACT OF CONCOMITANT CARDIOVASCULAR MEDICATIONS ON OVERALL SURVIVAL IN PATIENTS WITH LIVER CIRRHOSIS

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Background: Liver cirrhosis is the end-stage liver disease associated with poor prognosis. Cardiovascular comorbidity could significantly impact morbidity and mortality of cirrhotic patients. However, little knowledge exists for specific impact of diverse concomitant cardiovascular drugs in cirrhotic patients. Here, we conducted a large, retrospective study to investigate the survival impact of cardiovascular co-medications in patients with liver cirrhosis. **Methods**: A study-specific R package was processed on the local databases of partner institutions within the Observational Health Data Sciences and Informatics (OHDSI) consortium, namely Columbia University, New York City (NYC), U.S.A. and Ajou University School of Medicine (AUSOM), South Korea. For survival analysis, first diagnosis of cirrhosis was limited between 2000 and 2020. Final analysis of the anonymous survival data was performed at the Medical Faculty Mannheim. **Results**: We investigated a total of 32,366 patients with liver cirrhosis. Our data showed that administration of antiarrhythmics amiodarone or digoxin presented as a negative prognostic indicator ($p = 0.000$ in both cohorts). Improved survival was associated with angiotensin-converting enzyme inhibitor ramipril ($p = 0.005$ in NYC cohort, $p = 0.075$ in AUSOM cohort) and angiotensin II receptor blocker losartan ($p = 0.000$ in NYC cohort, $p = 0.005$ in AUSOM cohort). Non-selective beta blocker carvedilol was associated with a survival advantage in the NYC ($p = 0.000$) cohort but not in the AUSOM cohort ($p = 0.142$). Patients who took platelet inhibitor clopidogrel had a prolonged overall survival compared to those without ($p = 0.000$ in NYC cohort, $p = 0.003$ in AUSOM cohort). **Conclusion**: Liver cirrhosis is a complex chronic disease requiring multidisciplinary management. Concomitant cardiovascular medications used in cirrhotic patients are associated with distinct survival difference. Thus, a judicious choice of the proper cardiovascular co-medication in patients with cirrhosis is crucial.

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3443-A | IMPACT OF SAMPLING SIZE ON VARIABILITY OF FIBROSIS ASSESSMENT IN LIVER NEEDLE BIOPSIES USING SECOND HARMONIC GENERATION/TWO PHOTON EXCITATION MICROSCOPY AND ARTIFICIAL INTELLIGENCE ANALYSIS BASED FIBROSIS STAGING

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Background: Small liver biopsy increases the impact of sampling variability. Prior studies have defined minimum biopsy size for reliable assessment of fibrosis and informed guidelines for clinical trials in non-alcoholic steatohepatitis (NASH). Although digital pathology is increasingly employed in these trials, influence of sampling sizes on fibrosis assessment with this technology is poorly defined. We aimed to investigate the effect of sample size on quantification of fibrosis, qFibrosis (qF), and validate its impact on digital pathology readouts. **Methods:** 100 samples (taken from liver resections and explants), 20 each of pathologist-assigned NASH CRN - F0/F1/F2/F3/F4, were evaluated. Each sample was subjected to one virtual needle biopsy, fixed width 0.7mm, length between 5 and 20mm. qF stages were determined using Single Harmonic Generation/Two Photon Excitation (SHG/TPE) microscopy and artificial intelligence (AI)-based analysis. qF stage was compared with pathologist-assigned fibrosis stage and agreement was evaluated by calculating inter-observer Kappa values. Additionally, percentage cases where qF stage was higher or lower than pathologist's stage was calculated. **Results:** Analysis of Kappa values, both unweighted and weighted, showed greater concordance between qF and pathologist assessments as length of tissue samples increased. The Kappa values leveled off at 11mm upwards with asymptote around 15 mm, aligning with the current recommendations for pathologists (Table 1). Highest weighted Kappa value observed was 0.78, consistent with previously published inter-observer Kappa values. Percentage of cases where qF indicated higher fibrosis stages

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compared to pathologist assessments were greater when tissue length was shorter. Additional study of effects of other variables, including width and sample fragmentation, on accuracy of qF will also be presented at the meeting. **Conclusion:** In this systematic study, our findings demonstrate that qF tends to underestimate the extent of fibrosis in small biopsy sizes and a minimum tissue length of 15mm is required for qF to achieve reproducible agreement with pathologist's staging. This highlights the importance of considering minimum length of liver biopsy when utilizing qF as a clinical diagnostic tool.

Table 1: Concordance rates and percentage agreement rates for qF stage versus pathologist stage for different lengths of virtual biopsy

Tissue length	qF vs pathologist Unweighted Kappa	qF vs pathologist Linear weighted Kappa	%Cases (qF stage<pathologist stage)	%Case (qF stage>pathologist stage)
5 mm	0.43	0.63	27%	19%
6 mm	0.38	0.62	28%	22%
7 mm	0.39	0.63	27%	22%
8 mm	0.46	0.67	23%	20%
9 mm	0.53	0.70	19%	19%
10 mm	0.46	0.68	26%	17%
11 mm	0.51	0.71	21%	18%
12 mm	0.55	0.74	20%	16%
13 mm	0.59	0.77	17%	16%
14 mm	0.60	0.76	16%	16%
15 mm	0.60	0.75	15%	17%
16 mm	0.64	0.78	12%	17%
17 mm	0.63	0.78	13%	17%
18 mm	0.63	0.77	13%	17%
19 mm	0.61	0.76	14%	17%
20 mm	0.56	0.74	16%	19%

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3444-A | INDUCTION OF HEPATOCYTE NUCLEAR FACTOR 4 ALPHA (HNF4α) USING NOVEL EPIGENOMIC CONTROLLERS

Amy McCurley, Yoseph Kassa, Justin Chen, Wanzhu Zhao, Christopher Pedigo, Joseph Newman, Charles O'Donnell and Thomas McCauley, Omega Therapeutics

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

3513-C | ALCOHOL RELAPSE SCORES AND INDIVIDUAL SOCIAL DETERMINANTS OF HEALTH PREDICT ALCOHOL RELAPSE AFTER LIVER TRANSPLANT

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Background: Alcohol-associated liver disease (ALD) is a leading indication for liver transplant (LT) in the United States. Alcohol relapse is common and is associated with decreased post-LT survival. Risk scores have been used to predict relapse, however the impact of individual and area-level social determinants of health (SDOH) has not been fully explored. We hypothesize that SDOH are associated with post-LT alcohol relapse and survival. **Methods:** Adult patients with ALD who were transplanted at Indiana University Hospital from 9/2007 to 12/2021 with at least 6 months of follow-up were identified. Demographics, clinical characteristics, and alcohol use history were collected via chart review. Three relapse scores were calculated: High-Risk Alcoholism Relapse scale (HRAR), Alcohol Relapse Risk Assessment (ARRA) score, and Sustained Alcohol use post-LT (SALT) score. Six individual-level SDOH (marital status, living situation, education level, employment status, social security disability status and insurance type) and three area measures of deprivation (social deprivation index, area deprivation index, and % income below the federal poverty level) were collected. Multivariable logistic and Cox regression analyses were performed to identify factors associated with relapse and post-LT survival. **Results:** 405 patients underwent LT; mean age was 54.4 ± 8.4 years old, 22.2% were female and 4.7% were Black race. Mean MELD at time of LT was 19.4 ± 7; 25.4% had hepatocellular carcinoma (HCC) and 36.5% had psychiatric comorbidities. In regard to SDOH, 48.2% were married, 88.6% lived with another person, 20.7% did not complete high school, 23.7% were insured by Medicaid, and 24.1% lived in the most deprived quartile by area deprivation index. 53 patients relapsed to alcohol and 83 patients died during follow-up. On multivariable analysis, being unmarried, Medicaid insurance, and ARRA group (III/IV) were associated with higher odds of alcohol relapse (figure 1A). Medicare, HCC status, psychiatric comorbidities and HRAR score > (4+) were associated with increased risk of death (figure 1B). There was no significant association between area-level SDOH and alcohol relapse or post-LT survival. **Conclusion:** Alcohol risk scores and individual-level SDOH were associated with alcohol relapse and survival. Interventions to support this population should consider both, requiring a multidisciplinary approach.

Figure 1: Forest plot for multivariable analysis

Figure 1A: Risk factors for Alcohol Relapse

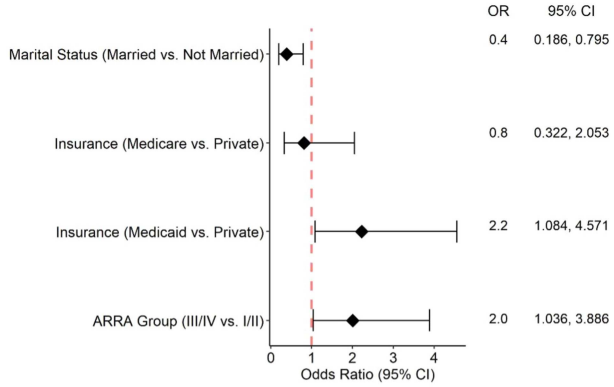
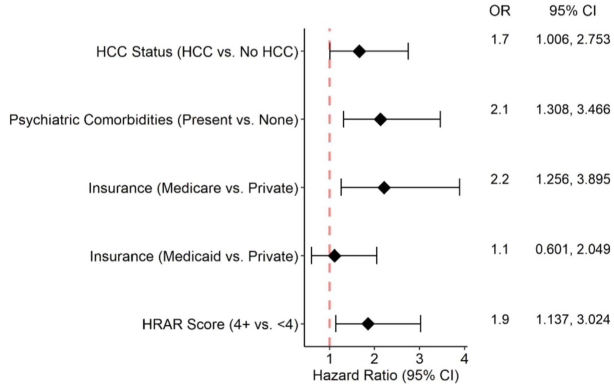


Figure 1B: Survival from Liver Transplant to Death



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3514-C | Alcohol use disorder treatment during COVID-19 among Veterans with cirrhosis

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Background: The COVID-19 pandemic has accelerated an already increasing prevalence of alcohol use disorder (AUD) and caused disruptions in already low rates of AUD adoption, particularly for women. Despite the growing number of women with alcohol-related liver diseases (ALD), there is limited research regarding AUD treatment patterns for women with liver disease. This study aimed to identify AUD treatment patterns among Veterans with cirrhosis, overall and specifically for women. **Methods:** Electronic health record data, including Veterans with two outpatient or one inpatient ICD-10 codes for cirrhosis and AUD between October 2019 and September 2022, was extracted from VA's Corporate Data Warehouse. AUD treatments (behavioral and pharmacotherapies) were identified using pharmacy data and validated combinations of ICD-10, Current Procedural Terminology (CPT), and stop codes. Multivariable logistic regression models, controlling for relevant demographics, liver-related conditions, and comorbidities, were used to identify factors associated with any AUD treatment and each type (behavioral and pharmacological), overall and stratified by gender. **Results:** Among 40,796 Veterans with cirrhosis and AUD, 3% were women, 40% had prior hepatic decompensation, and the mean MELD-Na score was 11 ± 6. Compared with men, women with AUD and cirrhosis were younger, with higher rates of homelessness, mental health and substance use disorders and lower comorbidity scores. Over a 180-day follow-up period, 3,371 individual's (8%) received any AUD treatment, 2,393 (6%) received pharmacotherapy alone, and 215 (0.5%) received both behavioral and pharmacotherapy. Women were less likely than men to receive any form of AUD treatment (adjusted odds ratio [AOR]: 0.8; 95% confidence interval [CI] 0.7 – 0.9; $p = 0.003$). Receipt of AUD treatment in the overall cohort was otherwise significantly associated with younger age (AOR 0.9; 95% CI 0.9 – 1.0, $p < 0.001$), homelessness (AOR 1.7; 95% CI 1.5 – 1.9, $p < 0.001$), co-occurring anxiety (AOR 1.7; 95% CI 1.5 – 1.9; $p < 0.001$), PTSD (AOR 1.6; 95% CI 1.4 – 1.8; $p < 0.001$), lower MELD-Na score (AOR 0.9; 95% CI 0.9 – 1.0; $p < 0.001$), and lower comorbidity score (AOR 0.9; 95% CI 0.9 – 1.0; $p < 0.001$). Odds of receiving pharmacotherapy were decreased for people who were non-Hispanic and Black (AOR 0.9; 95% CI 0.8 – 1.0; $p = 0.02$), but otherwise the models by type of AUD treatment were similar to the overall model. Factors associated with treatment were similar in models stratified by gender, except that pharmacotherapy was not significantly associated with race for women. **Conclusion:** During the COVID-19 pandemic, AUD pharmacotherapy accounted for a higher percentage of AUD treatment in VA patients with AUD and cirrhosis than previously described. The models defined key targets for intervention, including that women with AUD and cirrhosis were less likely than men to receive AUD treatment.

Table 1. Characteristics of Veterans with Alcohol-Use Disorder (AUD) and Cirrhosis by Gender, and AUD treatment status

	Men			Women		
	None	Any AUD Treatment	p-value	None	Any AUD Treatment	p-value
	N=36,436	N=3,233		N=987	N=138	
Age	69.5 (8.0)	65.9 (9.1)	<0.001	62.7 (8.8)	60.5 (8.2)	0.005
Race/Ethnicity			<0.001			0.74
White	21,802 (59.8%)	2,040 (63.1%)		583 (59.1%)	87 (63.0%)	
Hispanic	3,061 (8.4%)	279 (8.6%)		61 (6.2%)	6 (4.3%)	
Non-Hispanic Black	9,324 (25.6%)	745 (23.0%)		274 (27.8%)	35 (25.4%)	
Non-Hispanic Other	2,249 (6.2%)	169 (5.2%)		69 (7.0%)	10 (7.2%)	
Marital Status			<0.001			0.2
Married	11,656 (38.5%)	925 (34.9%)		223 (28.8%)	25 (22.9%)	
Div/Widowed	18,602 (61.4%)	1,724 (65.1%)		552 (71.2%)	84 (77.1%)	
Single	48 (0.2%)	1 (0.0%)		0	0	
Lack/Inadequate housing	14,346 (39.4%)	1,816 (56.2%)	<0.001	467 (47.3%)	80 (58.0%)	0.019
Prior Cirrhosis Decompensation	14,248 (39.1%)	1,533 (47.4%)	<0.001	427 (43.3%)	69 (50.0%)	0.14
MELD_Na	11.3 (6.1)	9.4 (4.2)	<0.001	10.4 (6.4)	9.4 (4.7)	0.2
Cannabis Use	5,622 (15.4%)	963 (29.8%)	<0.001	169 (17.1%)	43 (31.2%)	<0.001
Other Drug-related Diagnoses	8,564 (23.5%)	1,387 (42.9%)	<0.001	270 (27.4%)	57 (41.3%)	<0.001
AUDIT-C Score	1.9 (2.9)	5.8 (4.5)	<0.001	1.8 (3.1)	4.9 (4.3)	<0.001
Mood Disorder	18,747 (51.5%)	2,355 (72.8%)	<0.001	717 (72.6%)	123 (89.1%)	<0.001
Anxiety Disorder	11,773 (32.3%)	1,699 (52.6%)	<0.001	563 (57.0%)	97 (70.3%)	0.003
Schizophrenia	1,381 (3.8%)	179 (5.5%)	<0.001	44 (4.5%)	8 (5.8%)	0.48
PTSD	10,970 (30.1%)	1,521 (47.0%)	<0.001	443 (44.9%)	87 (63.0%)	<0.001
Charlson Comorbidity Index	4.5 (3.1)	3.8 (3.1)	<0.001	4.0 (2.6)	3.5 (2.5)	0.078

Data are presented as mean (SD) for continuous measures, and n (%) for categorical measures

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3515-C | ALCOHOLIC LIVER DISEASE AND CARDIAC ARRHYTHMIA

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

12% (275). ALD was seen in 1.2% (29) of the entire cohort and in 11% of those with hazardous alcohol use. Liver disease other than ALD was seen in 372 (16%) of the cohort. Among those with ALD, 17% (5/29) had CSF. PWHIV with ALD had higher median BMI (29 vs. 24 kg/m2, $p < 0.0001$), were more likely to be male (79% vs. 41%, $p < 0.0001$), have type 2 diabetes (17% vs. 6%, $p = 0.03$), and metabolic syndrome (55% vs 29%, $p = 0.008$) compared to those without liver disease. Furthermore, PWHIV with ALD had significantly higher LSM (median (IQR) 5.2 (4.4, 5.9) vs. 4.6 (3.8, 5.5), $p = 0.009$), and CSF (5 (17%) vs. 60 (3%), $p = 0.002$) compared to those without liver disease. **Conclusion:** In low to middle income countries, ALD is present in 1.2% of PWHIV and in 11% of PWHIV with hazardous alcohol use. A sizable proportion of PWHIV with ALD have evidence for clinically significant fibrosis. Metabolic syndrome may predispose PWHIV to ALD

Table comparing individuals with alcohol-associated liver disease and no liver disease

		ALD 29 (1.5%)	No Liver Disease 1932 (98.5%)	p-value
Demographics				
Age at enrolment	Median (Q1, Q3)	52.0(44.2,53.9)	50.3(45.3,56.1)	0.8520
Sex at birth	Male	23 (79)	788 (41)	<.0001
	Female	6 (21)	1144 (59)	
ARV Regimen	Integrase Inhibitors	7 (24)	758 (39)	0.0783
	NNRTI	8 (28)	734 (38)	
	Protease Inhibitors	6 (21)	192 (10)	
	Combined	3 (10)	141 (7)	
	Not Specified	5 (17)	107 (6)	
Clinical Features				
Hypertension	n(%)	9 (31)	425 (22)	0.24
Diabetes Type 2	n(%)	5 (17)	116 (6)	0.03
Dyslipidemia	n(%)	23 (79)	1484 (77)	0.76
Metabolic syndrome	n(%)	16 (55)	551 (29)	0.002
Body Mass Index (Kg/m^2)	Median (Q1, Q3)	29.2(27.1,32.9)	24.3(21.2,28.0)	<.0001
Excess Alcohol Use (AUDIT≥ 7[women] ≥8[men])	n(%)	29 (100)	230 (12)	<.0001
Vibration Controlled Transient Elastography (VCTE) by FibroScan				
Controlled Attenuation Parameter (CAP) [db/m)	Median (Q1, Q3)	309.0(294.0,335.0)	210.0(180.0,237.0)	<.0001
Liver stiffness Measurement (kPa)	Median (Q1, Q3)	5.2(4.4,5.9)	4.6(3.8,5.5)	0.009
Clinically significant fibrosis (LSM ≥8.6 kPa)	n(%)	5 (17)	60 (3)	0.0022
Laboratory Parameters				
Fasting Blood Glucose [mg/dL]	Median (Q1, Q3)	96.0(89.0,104.0)	90.0(81.0,98.0)	0.02
HbA1c [%]	Median (Q1, Q3)	5.4(5.0,5.9)	5.3(5.0,5.8)	0.51
Triglycerides (mg/dL)	Median (Q1, Q3)	154.0(72.7,206.0)	27.2(16.6,78.0)	<.0001
Lipid Panel:				
LDL[a] [mg/dL]	Median (Q1, Q3)	91.0(68.4,137.0)	54.0(39.6,79.4)	<.0001
HDL[a] (mg/dL)	Median (Q1, Q3)	41.0(25.2,48.0)	27.0(20.3,41.0)	0.01
ALT[a] (IU/L)	Median (Q1, Q3)	33.0(24.3,43.0)	21.0(16.0,28.0)	<.0001
AST[a] (IU/L)	Median (Q1, Q3)	28.3(24.0,36.2)	26.0(21.0,31.4)	0.03
ALP[a] (IU/L)	Median (Q1, Q3)	84.0(69.0,129.0)	89.0(71.6,116.0)	0.75
GGTP (IU/L)	Median (Q1, Q3)	48.6(42.3,62.0)	32.0(21.0,49.0)	0.0002
Platelets (10^3/uL)	Median (Q1, Q3)	254.0(183.0,288.0)	246.0(206.0,297.0)	0.59

[a]**Abbreviations:** Antiretroviral Therapy (ART); Integrase Inhibitors (II), Non-nucleoside reverse transcriptase inhibitors (NNRTI), Protease Inhibitors (PI); Low density lipoprotein (LDL); High density lipoproteins (HDL); Alanine aminotransferase (ALT); Aspartate aminotransferase (AST); Alkaline phosphatase (ALP); Gamma-glutamyl transferase (GGT)

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♦ 3517-C | ALCOHOL-RELATED ETIOLOGY IS AN INDEPENDENT PREDICTOR OF INPATIENT MORTALITY IN PATIENTS WITH CIRRHOSIS IN A PROSPECTIVE GLOBAL CONSORTIUM

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Background: The burden of cirrhosis, especially due to alcohol and metabolic factors is increasing, more so during the pandemic period. However, the impact of these various etiologies of cirrhosis across different regions of the world remains unclear. **Methods:** The multi-national CLEARED consortium prospectively enrolled in-patients with cirrhosis without COVID-19 and followed them for 30-days post-discharge. Etiology related to alcohol, NASH, HCV, HBV, Autoimmune and others were studied with respect to presentation, decompensation, complications, course in hospital and survival at 30-days post discharge across all 6 continents. **Results:** Total of 4238 patients from 107 centers in 27 countries were included. The predominant etiology was alcohol (1689,39.5%) followed by NASH/ Cryptogenic (913,21.5%), HBV (751, 17.7%), auto-immune (396,9.3%) and HCV (299,5.4%). Ethanol was commoner in men (78.6%), NASH was gender balanced (55%) and AILD (24%) mainly in females. Patients with alcohol-related cirrhosis (ARC) had more advanced cirrhosis [prior HE (45.6%), refractory ascites

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(40.9%), hospitalization (40.6%)] than other etiologies ($p < 0.001$), but had lower listing for LT. Alcohol related Cirrhosis patients were admitted with higher MELD-Na 23 (IQR 17-29) vs 21 (IQR15-27). Infection at admission, SBP, GI Bleed, HE, AKI and anasarca were more likely seen in ARC than other etiology significantly (Figure). The hospital stay of Alcohol related Cirrhosis patients was accompanied by more complications due to higher nosocomial infection, in-hospital AKI, ICU transfer and in-patient mortality. There were 104(2.5%) in-hospital transplants, of which fewer were done among ARC patients than others [NASH (12.5% vs 31.7%) and they were sicker with a higher baseline MELD Na of 23 (IQR 17-29) and at discharge 21 (IQR 15-27) than others ($p < 0.001$). During follow-up, the 30 days readmission and mortality was higher with ethanol. Transplant (ethanol-39.2%, NASH-27.6%, Viral 11.6%, AILD 11.6%, $P < 0.001$) rate was better of the total 81(5.5%) within 30days of discharge ($p < 0.001$). In multivariate analysis, the inpatient mortality was higher in ARC vs HCV, OR 1.07(0.65-1.76), NASH, OR 1.41 (1.06-1.89), and AILD, OR 1.79(1.23-2.59), $p < 0.003$). On the other hand, HBV related cirrhosis had a lower in-hospital mortality (5.6% vs 11.1 average, $p < 0.01$) and were at lower risk of in-hospital death compared to ARC patients [OR 0.55(0.37-0.83, $p < 0.003$]. **Conclusion:** In a prospective global cohort of inpatients with cirrhosis, alcohol related cirrhosis remains the most common etiology across the world. The alcohol related cirrhosis associated with more severe disease, higher in-hospital complications, mortality and lower in-hospital likelihood of getting a liver transplant. Alcohol-related liver diseases deserve special focus, monitoring during and after discharge and early liver transplant, across the world.

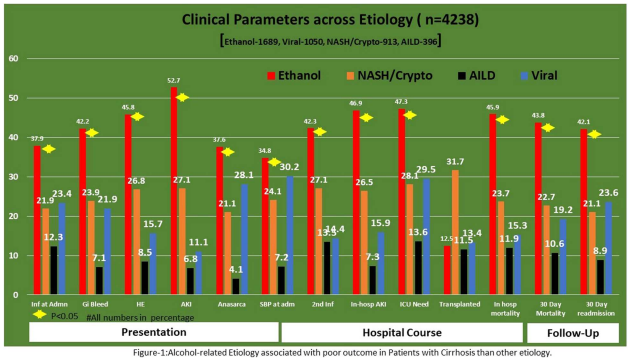

Figure-1:Alcohol-related Etiology associated with poor outcome in Patients with Cirrhosis than other etiology.

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3518-C | AMOUNT OF ALCOHOL CONSUMPTION AND MORTALITY IN WOMEN WITH ALCOHOL-RELATED CIRRHOSIS.

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66.2% of patients were men, 79.4% of patients were white, the median age was 60 years, and median follow-up was 6.6 years. Among these patients 8,873 (70.8%) had normal findings, 2,334 (18.6%) showed features of steatosis, and 1,220 (9.7%) had radiologic cirrhosis on their first image. In our cox regression model, fatty liver on first liver imaging was associated with increased rate of ALD (HR, 3.63; 95% CI, 3.1-4.1; $P < 0.001$). Among patients with AUD, male gender, hypertension, chronic kidney disease (CKD) and diabetes were also associated with increased rate of ALD, while hyperlipemia was associated with 46% decreased risk (HR, 0.54; 95% CI, 0.5-0.6; $P < 0.001$). **Conclusion:** The findings of this study suggest image evidence of fatty liver disease in AUD patients can serve as early detection for progression of advanced liver disease. Appropriate integration of radiological data and early intervention in this population are likely to optimize patient outcomes.

	ALD events (n = 943)	sHR (95% CI)	P-value
Variables			
Steatosis on First Image	438	3.6 (3.1-4.1)	<0.001*
Male Gender	704	1.2 (1.0-1.4)	0.013*
CKD	250	1.6 (1.3-1.8)	<0.001*
HTN	582	1.3 (1.1-1.5)	0.003*
Diabetes	264	1.2 (1.0-1.4)	0.013*
Hyperlipidemia	428	0.54 (0.5-0.6)	<0.001*
COPD	363	0.91 (0.8-1.1)	0.255
Tobacco Use Disorder	485	0.98 (0.9-1.1)	0.793
Ischemic Heart Disease	280	1.0 (0.9-1.2)	0.872
Stroke	177	0.98 (0.8-1.2)	0.787

Disclosures: The following people have nothing to disclose: Jibril F. Kedir, Rachael Mahle, Wei Zhang
Disclosure information not available at the time of publication: Adedayo Okanlawon, Russell P. Goodman, Esperance Schaefer, Jay Luther

3536-C | DIAMMONIUM GLYCYRRHIZINATE PROTECTS AGAINST ETHANOL INDUCED LIVER INJURY VIA INHIBITING DDX5/STAT1 PATHWAY

Xiaomei Wang, Hongqin Xu and Xiuzhu Gao, The First Hospital of Jilin University

Background: Alcoholic liver disease (ALD) is a serious worldwide health problem. Diammonium glycyrrhizinate (DG) is a medicinal form of glycyrrhizic acid (GA) extracted from licorice roots with anti-inflammatory properties. Some of its beneficial effects in vivo are reported to involve viral hepatitis. Here, we evaluated the potential and the possible mechanism of DG protecting against ethanol-induced liver injury in vitro and in vivo. **Methods:** We investigated the effects of DG on liver lipid metabolism, oxidative stress, and inflammation, induced by chronic plus binge alcohol feeding in mice in vivo by using biochemical assays, qPCR, and histology analyses. Analyses of RNAseq expression were conducted to explore potential targets exploited by DG to protect against ALD. In vitro, mouse cell line, AML12 cells were treated with DG (50μM) prior to ethanol (400 mM) for 24 h. Cell viability was analyzed by CCK8, and protein expressions were assessed by Western blot. **Results:** Chronic treatment with DG alleviated the chronic and binge alcohol-induced liver injury and inflammation, as well as the lipid deposition in hepatocytes. It also beneficially influenced hepatic metabolic and oxidative stress dysregulation. Mice liver tissue RNAseq expression indicated that DEAD-box protein 5 (DDX5) may be a potential target exploited by DG to protect against ALD. The expression of DDX5 was significantly reduced in the ethanol-treated group, following the downregulation of signal transducer and activator of transcription 1 (STAT1), and DG increased the expression of DDX5 and STAT1. These protective effects of DG against alcohol-induced liver injury were attenuated in DDX5 deficient cell line, indicating the beneficial effects of DG in ethanol-induced liver injury by up-regulating the DDX5/STAT1 pathway. **Conclusion:** DG prevented ethanol-induced hepatic injury associated with oxidative stress, inflammation, and steatosis via up-regulating the DDX5/STAT1 pathway.
Disclosures: The following people have nothing to disclose: Xiaomei Wang
Disclosure information not available at the time of publication: Hongqin Xu, Xiuzhu Gao

3537-C | DIFFERENCES IN THE CLINICAL PRESENTATION OF ACUTE ALCOHOLIC HEPATITIS BETWEEN CAUCASIANS AND AFRICAN AMERICANS

Yiwei Hang[1], Marcus Allen Healey[1], Geetha Ramalingam[1], Ekaterina Smirnova[2], Amon Asgharpour[3], Vaishali Patel[4], Hannah Lee[4], Velimir A. Luketic[2], Scott C. Matherly[4], Mohammad S. Siddiqui[4], Joel P. Wedd[4], Arun Sanyal[5] and Richard K. Sterling[4], (1)VCU Health, (2)Virginia Commonwealth University, Richmond, VA, (3)Virginia Commonwealth University, (4)Virginia Commonwealth University Health System, (5)Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA

Background: Acute alcoholic hepatitis (AAH) incurs high morbidity and mortality. While differences in survival between African Americans (AA) and Caucasians have been reported, the use of steroids and disease severity upon admission are unknown. To address this gap, we aim to investigate the difference in clinical presentation and outcomes between AAs and Caucasians hospitalized for AAH to better understand the existing health disparities in AAH and help inform guidelines related to disease management. **Methods:**

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

In this retrospective analysis, patients admitted for AAH from 2012-2019 were identified and recorded in RED-Cap. Those with repeated admissions were excluded. Chart review was performed to collect data on demographics, disease characteristics, and clinical course. The diagnosis of AAH was verified using the National Institute on Alcohol Abuse and Alcoholism criteria. The primary outcomes were disease severity based on Model for End-Stage Liver Disease (MELD) and discriminant function (DF) at time of admission, the use of steroids, and 30-day (30-d) survival between Caucasians and AAs. **Results:** In total, 550 Caucasian and 245 AA patients were included in the analysis (Table 1). AAs were 5.2 years older on average. Liver markers such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin and international normalized ratio (INR) did not differ, but total bilirubin (TB) was lower in the AA group. Co-morbid conditions were similar except for the higher prevalence of hepatic C virus (HCV) in AA patients. While the MELD score did not vary between the two cohorts, the DF was significantly higher in Caucasian patients. Similarly, Caucasians were more likely to receive steroids than AA patients. The 30-d survival and days of hospitalization did not differ significantly between the two groups. In the multivariable model, increased weight ($p = 0.03$), higher MELD ($p < 0.001$), steroid use ($p = 0.029$), and presence of HCV antibody ($p = 0.04$) were significant predictors of 30-day survival while race was not ($p = 0.7$). **Conclusion:** AAH remains an important cause of liver-related mortality in the United States. In our urban cohort, AA patients were older, presented with less severe AAH by DF with similar MELD, and were less likely to receive steroids. However, there was no difference in survival and length of stay. This highlights the disparity in AAH by race and a need for specific treatment guidelines to manage future patient care in this population.

	Caucasian	African American	p-value
# patients	550	245	
Age (years)	47.3 (11)*	52.7 (10)	<.0001
% Male	44	39	
Weight (kg)	86 (26)	82 (24)	0.09
AST	521	386	0.4
ALT	131	158	
Total bilirubin	13 (11)	9.4 (10)	0.002
Albumin (g/dL)	2.8 (0.6)	2.7 (0.7)	
PT (sec)	21.4 (7.4)	20.9 (7.6)	.08
INR	1.88 (0.9)	1.82 (0.9)	
Cr (mg/dl)	1.35 (1.33)	1.44 (1.4)	0.1
MELD score	20.7 (10)	19 (11)	0.07
DF (using PT of 12)	56 (37)	50 (39)	.02
DF>=32 (%)	74	56	<.001
HE (%)	14	11	
DM (%)	16	23	.07
HBV (%)	1	1	
HCV (%)	10	19	.0085
Ascites (%)	3	4	
GI bleed (%)	3	6	
Bacteremia (%)	2	5	
History of bariatric surgery (%)	7	4	
Steroid use	51	30	<.001
30 Day Survival (%)	86	85	
Hospitalization days	10 (12)	9.6 (12)	

Disclosures: Amon Asgharpour – Galectin: Consultant, No, No;
Arun Sanyal – Durect: Stock – privately held company (individual stocks and stock options), No, No; GenFit: Stock – privately held company (individual stocks and stock options), No, No; Gilead: Consultant, No, No; Novartis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genetech: Consultant, No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Path-AI: Consultant, No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Histoindex: Consultant, No, No; Fibronest: Consultant, No, No; Hemoshear: Stock – privately held company (individual stocks and stock options), No, No; Hemoshear: Consultant, No, No; Inversago: Stock – privately held company (individual stocks and stock options), No, No; Biocellvia: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Eli Lilly: Consultant, No, No; Novo Nordisk: Consultant, No, No; Boehringer Ingelheim: Consultant, No, No; Astra Zeneca: Consultant, No, No; Boehringer Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Akero: Consultant, No, No; Intercept: Consultant, No, No; Fractyl: Consultant, No, No; Madrigal: Consultant, No, No; Northsea: Consultant, No, No; Takeda: Consultant, No, No; Regeneron: Consultant, No, No; Eli Lilly: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Alnylam: Consultant, No, No; Novo Nordisk: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Consultant, No, No; Glaxo Smith Kline: Consultant, No, No; Novartis: Consultant, No, No; Tern: Consultant, No, No; Inventiva: Consultant, No, No; Target Pharmasolutions: Consultant, No, No; Tiziana: Stock – privately held company (individual stocks and stock options), No, No; Uptodate: Royalties or patent beneficiary, No, No; Elsevier: Royalties or patent beneficiary, No, No; Merck: Grant/Research Support (research funding from ineligible companies

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The following people have nothing to disclose: Yiwei Hang, Marcus Allen Healey, Geetha Ramalingam, Ekaterina Smirnova, Vaishali Patel, Hannah Lee, Scott C. Matherly, Mohammad S. Siddiqui, Joel P. Wedd, Richard K. Sterling
Disclosure information not available at the time of publication: Velimir A. Luketic

3538-C | DIFFERENTIAL ORIGINS AND FUNCTIONS OF CD163+ AND CD163- KUPFFER CELLS IN A MOUSE MODEL OF ALCOHOL-ASSOCIATED LIVER DISEASE

Sheetalnath Rooge[1,2], Isabel Aranzazu Pulido Ruiz[2], Kyo Sasaki[3], Kyle Yuquimpo[4], Heer Mehta[4], Ann Wozniak[2], Irina Tikhanovich[2], Sumedha Gunewardena[4] and Steven A. Weinman[5], (1)University of Kansas Medical Center, Kansas City, KS, (2)University of Kansas Medical Center, (3)Kawasaki Medical School, (4)University Kansas Medical Center, (5)University of Kansas Medical Center, Mission Hills, KS

Background: The liver macrophage pool consists of both embryonic-derived Kupffer Cells (eKCs) and infiltrating monocyte/macrophages (IMs). During disease states, these populations are dynamic with some eKCs replaced by monocyte-derived mKCs. We previously showed that replacement of CD163+ eKCs with newly formed CD163- mKCs leads to liver failure suggesting that eKCs are required for maintenance of liver function. The **Aim** of this study was to identify the origin, stability and function of KC subsets in ALD. **Methods:** C57BL/6J mice were fed a high fat (WD) diet with ad-libitum 10%-20% alcohol in the drinking water for 16 to 52 weeks (WDA model). Cx3Cr1-ER-Cre x Rosa26-mT/mG lineage tracer mice were used to evaluate the origin of KC subsets. scRNAseq was performed on total liver CD45+ cells isolated from the WDA mice model. Co-culture experiments were performed to evaluate the hepatoprotective properties of KCs. **Results:** Abundance of CD163+ KCs declined from 90% to 75% to 5% of total KCs at 0, 16 and 52 weeks of WDA diet, respectively. Tamoxifen injection of Cx3Cr1-ER-mT/mG tracer mice resulted in labeling of IMs and CD163- KCs at 1 week, but CD163+ cells remained unlabeled. At 4 weeks after injection, there was still no appearance of label in the CD163+ KCs demonstrating that they did not arise from CD163- KCs. scRNAseq with RNA velocity analysis showed that KC and IM cell identity was stable in chow-fed mice. In both WD and WDA mice, cell identity was in flux and IMs were direct precursors of CD163- KCs. In the absence of alcohol (WD only), CD163- KCs further transitioned to form CD163+ KCs, but in the presence of alcohol this transition was slowed suggesting a block of new KC maturation. Co-culture of isolated hepatocytes with CD163+ KCs preserved hepatocyte albumin production while CD163- KCs lacked this hepatoprotective effect. Gene set enrichment analysis showed that CD163+ KCs most resembled macrophages associated with hepatoprotection and fibrosis resolution while CD163- KCs most resembled lipid-associated macrophages (LAMs). **Conclusion:** CD163 expression identifies a KC subset that is largely embryonic in origin, is antifibrotic, and is critical for support of liver function during alcohol exposure. With increasing time of alcohol exposure, these KCs are progressively replaced by monocyte-derived CD163- KCs that are less hepatoprotective. We propose that loss of protective KCs may contribute to alcohol induced ACLF, as occurs in alcoholic hepatitis.
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Disclosure information not available at the time of publication: Isabel Aranzazu Pulido Ruiz, Kyle Yuquimpo, Heer Mehta, Ann Wozniak, Sumedha Gunewardena

3539-C | Drp1 REGULATES GSDMD MEDIATED MITOCHONDRIAL DYSFUNCTION AND HEPATOCYTE PYROPTOSIS IN AH

Yan-Di Xie[1], Zilong Wang[2], Guangjun Song[1], Hui Ma[1] and Bo Feng[1], (1)Peking University People's Hospital, (2)Peking University People's Hospital, Peking University Hepatology Institute, Beijing Key Laboratory of Hepatitis C and Immunotherapy for Liver Diseases, Beijing International Cooperation Base for Science and Technology on NAFLD Diagnosis

Background: Mechanisms and consequences of Gasdermin D (GSDMD) activation in alcoholic hepatitis (AH) are unclear. In the present work, we investigated whether dynamin-related protein 1 (Drp1) regulates GSDMD mediated mitochondrial dysfunction and hepatocyte pyroptosis in AH. **Methods:** Liver damage in AH mice were assessed by HE staining, serum levels of

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

Qaiser Shahzad, Aidan Farrell, Muhammad Umair Akmal, RIda Mah Noor, Reza Akhtar, Mohammad Hossain, Arif Asif

3564-C | IMPACT OF BARIATRIC SURGERY ON SEVERITY AND OUTCOMES IN ACUTE ALCOHOLIC HEPATITIS

Marcus Allen Healey[1], Geetha Ramalingam[1], Yiwei Hang[1], Ekaterina Smirnova[2], Amon Asgharpour[3], Vaishali Patel[4], Hannah Lee[4], Velimir A. Luketic[2], Scott C. Matherly[4], Mohammad S. Siddiqui[4], Joel P. Wedd[4], Arun Sanyal[5] and Richard K. Sterling[4], (1)VCU Health, (2)Virginia Commonwealth University, Richmond, VA, (3)Virginia Commonwealth University, (4)Virginia Commonwealth University Health System, (5)Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA

Background: Bariatric surgery (BS) is increasingly used to treat morbid obesity and is associated with higher incidence of alcohol use disorder (AUD) and acute alcoholic hepatitis (AAH). However, whether BS causes more severe presentations of AAH is less well-defined. Our aim is to compare the severity of AAH among hospitalized patients to contemporaneous matched controls from the same time period. **Methods:** Retrospective chart review of 35 hospitalized patients with AAH and prior BS and age, gender, and BMI matched (2:1) controls from 2012-2019 was performed. All values were obtained on date of index admission, except for Model for End-Stage Liver Disease (MELD) recorded both at admission and upon discharge. Demographics were obtained including age, race, sex, ethnicity, weight, and body mass index (BMI). Laboratory markers were obtained and included aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), international normalized ratio (INR), prothrombin time (PT), albumin and creatinine (Cr). Steroid administration and thirty-day (30-d) survival were compared. To define severity of AAH, both Maddrey's Discriminant Function (MDF) and MELD were calculated. **Results:** Of the BS cohort, 25/35 had Roux-en-Y performed. The demographic and clinical characteristics of BS patients and 76 controls are found in Table 1. Among laboratory parameters, those with history of BS had higher TB, PT, INR, and Cr. However, only the TB ($p = 0.017$) and albumin ($p = 0.0001$) were significantly different. Patients with BS were found to have more severe AAH when using MDF to define severity ($p = 0.026$) at all ranges of control PT values (12, 13.5, 14.8). However, when using MELD on admission and discharge, the severity of AAH between those with and without BS was not statistically significant ($p = 0.380$ and $p = 0.923$, respectively). While steroid administration was higher in the BS group ($p = 0.03$), adjusted 30-d survival was not different between those with and without BS ($p = 0.075$). **Conclusion:** Our study shows that compared to matched controls, the severity of AAH in those with prior BS is increased when using MDF, but not when using MELD. While those with BS were more likely to receive steroids for AAH due to higher MDF (due to higher TB), they had similar MELD and 30-d survival. Thus, future research into the role of these tests in AAH is needed to define the primary score to elucidate severity and pathogenesis in this unique population.

S.No	Contents	Bariatric Surgery "Yes".	Bariatric Surgery "No".	Odds Ratio	Confidence interval	P-value
1.	Number of subjects (Roux-en-Y/Unspecified)	35 (25/10)	76		-	-
2.	Age in years	45.9 (9.32)	44.0 (12.0)		-6.025567,2.284965	0.3733
3.	Male/Female	7/28	16/60		-	-
4.	Race (AA/W/unknown)	6/28/1	9/63/4		-	-
5.	Ethnicity % non-Hispanic	85.71%	87.47%		-	-
6.	Weight in kg	96.0(21.4)	76.4 (21.8)		-28.40989, -10.82171	3.266e-05
7.	BMI kg/m2	34.0 (7.29)	37.2 (42.2)		-11.05797, 17.45940	0.6573
8.	AST U/L	211 (92.5)	272 (255)		-27.25495, 149.26190	0.1735
9.	ALT U/L	70.4 (46.2)	88.3 (82.2)		-11.67392, 47.50640	0.2327
10.	Total bilirubin mg/dL	17.8 (12.5)	11.8 (10.4)		-10.879818, -1.114546	0.01696
11.	Albumin g/dL	2.53 (0.429)	2.92 (0.646)		0.1575553, 0.6339505	0.001341
12.	PT sec	20.2 (5.33)	19.4 (4.58)		-2.921650, 1.282919	0.4386
13.	INR	1.76 (0.577)	1.65 (0.474)		-0.3307588, 0.1192508	0.3506
14.	Creatinine mg/dl	1.13 (0.802)	0.989 (0.801)		-0.4676956, 0.1886609	0.3991
15.	DF (using PT of 12)	55.5 (30.8)	40.6 (34.8)		-27.985228, -1.864501	0.02568
16.	DF (using PT 13.5)	48.6 (30.8)	33.7 (34.8)		-27.985228, -1.864501	0.02568
17.	DF (using PT 14.8)	42.7 (30.8)	27.7 (34.8)		-27.985228, -1.864501	0.02568
18.	MELD (admission)	21.3 (9.99)	19.5 (9.67)		-5.857679, 2.260818	0.3795
19.	MELD (discharge)	23.7 (9.62)	24.1 (25.4)		-8.514347, 9.388297	0.9231
20.	FIB-4	7.26 (3.58)	10.2 (9.47)		-0.4276469, 6.2521141	0.08673
21.	Thirty-day survival rate	82.85%	93.42%	0.2966234	0.06560764 1.27494350	0.07489
22.	Steroid administration	77.14%	50%	2.755654	1.040227, 7.992760	0.03325

Disclosures: Amon Asgharpour – Galectin: Consultant, No, No;
Arun Sanyal – Durect: Stock – privately held company (individual stocks and stock options), No, No; GenFit: Stock – privately held company (individual stocks and stock options), No, No; Gilead: Consultant, No, No; Novartis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genetech: Consultant, No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Path-AI: Consultant, No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Histoindex: Consultant, No, No; Fibronest: Consultant, No, No; Hemoshear: Stock – privately held company (individual stocks and stock options), No, No; Hemoshear: Consultant, No, No; Inversago: Stock – privately held company (individual stocks and stock options), No, No; Biocellvia: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Eli Lilly: Consultant, No, No; Novo Nordisk: Consultant, No, No; Boehringer Ingelheim: Consultant, No, No; Astra Zeneca: Consultant, No, No; Boehringer Ingelheim: Grant/Research Support (research

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The following people have nothing to disclose: Marcus Allen Healey, Geetha Ramalingam, Yiwei Hang, Ekaterina Smirnova, Vaishali Patel, Hannah Lee, Scott C. Matherly, Mohammad S. Siddiqui, Joel P. Wedd, Richard K. Sterling
Disclosure information not available at the time of publication: Velimir A. Luketic

3565-C | IMPACT OF CHRONIC ETHANOL CONSUMPTION AND SARS-COV-2 ON THE GUT-LIVER AXIS IN MICE: A PILOT DOSE-RESPONSE STUDY

Smita Ghare[1], Dennis Warner[1], Josiah Hardesty[1], Jeffrey Warner[1], Paula Chilton[1], Jiyeon Lee[1], Jingwen Zhang[1], Lihua Zhang[1], Min Wan[1], Jon Gabbard[1], Charles Anderson[1], Lalit Batra[1], Chithra Sreenivasan[1], Jennifer Kraenzle[1], Matthew McCulley[1], Stephanie McCoy[1], Dibson Dibe Gondim[1], Shirish Barve[1], Wenke Feng[1], Jian Zheng[1], Kenneth Palmer[1], Craig J. McClain[1,2] and Irina A. Kirpich[1], (1)University of Louisville, Louisville, KY, (2)Robley Rex VAMC

Background: During the COVID-19 pandemic, there was a marked increase in alcohol consumption. COVID-19 superimposed on underlying liver disease notably worsens the outcome of many forms of liver injury. The goal of this study was to examine the impact/potential mechanistic interactions of ethanol (EtOH) and COVID-19 on the gut-liver axis in an experimental alcohol-associated liver disease. **Methods:** After 5 weeks of EtOH feeding, C57BL/6 male mice received SARS-CoV-2 (SARS2-N501Y$_{MA30}$) intranasally at $3x10^2$, 10^3, $3x10^3$, and $3x10^4$ plaque-forming units (PFU). Mice were then weighed/monitored daily for morbidity/mortality for 12 days while continuing EtOH consumption. Liver injury, intestinal barrier integrity, and systemic inflammation were evaluated. The study was conducted within a Biosafety Level 3 facility. **Results:** A similar gradual weight loss was observed in all inoculated mice (slightly less in the $3x10^2$ group) up to post infection day 4 (Fig. 1A). Greater mortality was observed in mice receiving the highest viral dose at days 3 and 4 post infection (20% and 26%, respectively. Fig. 1B). There was variable mortality in mice inoculated with $3x10^3$ and 10^3 PFU (22% and 5% at day 4, respectively). Most mice in these groups were euthanized at day 5 due to 25% loss of weight. There was no mortality in mice receiving the lowest dose, and these mice were euthanized at day 11-12 post infection. Analysis of liver health revealed no significant changes in hepatic steatosis and a limited increase in plasma ALT levels at all viral doses *vs.* EtOH alone. However, there was an increase in TUNEL$^+$ and CAE$^+$ cells (markers of hepatocyte death and neutrophil infiltration) in livers in all but the lowest dose. Further, the highest viral dose elevated hepatic mRNA levels of several pro-inflammatory cytokines and markers of ER stress (e.g., *Il-6*, *Tnf-α* and *Atf3,* respectively). In addition, compared to EtOH alone, EtOH+SARS2-N501Y$_{MA30}$ decreased plasma IL-22 and IL-10 with the lowest levels in mice with the highest viral challenge. Lastly, in EtOH fed mice, the highest viral dose lowered expression of intestinal tight junction proteins, *Zo1*, *Cldn-5* and *Ocln*, and the antimicrobial protein *Cramp1*. **Conclusion:** We developed a unique animal model of SARS-CoV-2 and chronic EtOH consumption. This pilot study suggests that early mortality observed after high dose SARS-CoV-2 challenge could be due in part to hepatic and intestinal damage/dysfunction following chronic EtOH feeding.

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

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3567-C | IMPAIRED CHAPERONE-MEDIATED AUTOPHAGY CONTRIBUTES TO HEPATIC LIPID DROPLET ACCUMULATION IN ALCOHOL-FED RODENTS

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Background: Alcohol-induced fatty liver disease is characterized by the accumulation of lipid droplets (LDs) in liver cells, impairing their normal function. Autophagy, a cellular recycling process, plays a crucial role in eliminating LDs from cells, with lysosomes serving as the final destination. In this study, we investigated the impact of chronic ethanol (EtOH) feeding on chaperone-mediated autophagy (CMA) and its association with hepatic LD accumulation. **Methods:** Mice and rats were subjected to either chronic binge EtOH or chronic EtOH feeding, while EtOH-metabolizing VA-13 cells were used for *in vitro* experiments **Results:** Hepatocytes from EtOH-fed rats displayed significantly larger LDs compared to controls. Immunostaining revealed the close association of LDs with LAMP2A, a marker of CMA-positive lysosomes, and HSC-70, an essential chaperone for CMA cargo targeting. Immunoblotting analysis showed a 1.5-fold decrease in hepatic LAMP2A levels in chronic binge EtOH-fed mice, concomitant with a 2.5-fold increase in hepatic triglycerides and a 7-fold elevation in serum ALT levels. Importantly, purified lysosomes from chronic EtOH-fed mice exhibited a 20% reduction in the ability to degrade exogenously added CMA substrate ribonuclease *in vitro*. Notably, treating EtOH-metabolizing VA-13 cells with the CMA activating agent AR7 resulted in a 1.6-fold induction of cathepsin B activity and a 2-fold increase in lysosomal acid lipase activity compared to untreated cells, accompanied by a reduction in LD staining. **Conclusion:** Collectively, our findings demonstrate that CMA-positive lysosomes and associated chaperones play a crucial role in targeting LDs for degradation. However, chronic EtOH feeding compromises the lysosomes' capacity to perform CMA, leading to the intracellular accumulation of LDs and consequent fatty liver development. Notably, selectively activating CMA with pharmacological agents such as AR7 shows promise in alleviating EtOH-induced fatty liver.
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3568-C | INCIDENCE OF ACUTE KIDNEY INJURY IN PATIENTS WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS – DATA FROM A MULTICENTER CLINICAL TRIAL OF ANAKINRA PLUS ZINC VS. PREDNISONE

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Background: Acute kidney injury (AKI) is associated with poor survival in severe alcohol-associated hepatitis (sAH) patients. Clinical characteristics of AKI have not been well-characterized in sAH treated with IL-1β antagonist anakinra+zinc (AZ) in comparison to prednisone (pred). Therefore, we aimed to compare the incidence, staging, and phenotype of AKI between AZ and pred-treated patients. **Methods:** 147 patients in a multicenter clinical trial for sAH comparing AZ and pred were analyzed. AKI and its stages were defined by Kidney Disease Improving Global Outcomes consensus definitions. AKI phenotypes (pre-renal, acute tubular necrosis, hepatorenal syndrome) were determined by two blinded adjudicators and a tiebreaker in case of disagreements. Baseline characteristics between patients who did/did not develop AKI in the two treatment arms were compared. Urinary kidney injury markers [KIM1, IL18, NGAL, and LFABP) were also compared between treatment arms at days 0, 7, 14, and 28. **Results:** No patients had AKI at baseline and 33% (n = 49) developed AKI. AZ-treated patients had significantly higher rates of AKI development compared to pred-treated patients, 45% (n = 33) vs. 22% (n = 16), p = 0.004. Baseline characteristics in patients who did/did not develop AKI in each treatment arm are shown in the Table. Patients who did/did not develop AKI in each treatment arm had similar baseline MELD (p = 0.168) and Maddrey Discriminant scores (p = 0.523), and had similar baseline creatinine (p = 0.431). Compared to pred-treated patients, AZ-treated patients had more severe AKI stages at diagnosis [stage 2/3 n = 21 (64%) vs. n = 5 (31%), p = 0.033] and at peak [stage 2/3 n = 29 (88%) vs. n = 9 (56%), p = 0.025]. The frequency of AKI phenotypes was similar between the two treatment arms (p = 0.515), with acute tubular necrosis being the most common phenotype (42% AZ vs. 38% pred) followed by pre-renal (15% AZ vs. 31% pred). AZ-treated patients who developed AKI had significantly higher Day 7 urinary NGAL levels compared to patients without AKI in both treatment arms (p = 0.015) but was similar to pred-treated patients with AKI (p = 0.071). There were no significant differences between each treatment arm for NGAL on Days 0, 14, and 28. Similarly, there were no significant differences between treatment arms for KIM1, IL18, and LFABP on days 0, 7, 14, and 28. **Conclusion:** AKI was a common complication in sAH patients treated with pred or AZ but occurred more frequently and was more severe in AZ-treated patients. Further studies are needed to understand the mechanisms driving AKI development in sAH, as further insight may help with future treatment/prevention of AKI in sAH.

Table: Comparisons of Baseline Patient Characteristics Stratified by AKI development in Each Treatment Arm.

Baseline Patient Characteristics	Prednisone (n=73)		Anakinra/Zinc (n=74)		P-value
	AKI N=16	No-AKI N=57	AKI N=33	No-AKI N=41	
Age	46.6 ± 12.3	44.4 ± 10.0	44.4 ± 9.3	44.6 ± 9.4	0.884
Sex, n (%) Male	11 (68.8%)	30 (52.6%)	19 (57.6%)	28 (68.3%)	0.384
Race, n (%) White	15 (93.8%)	46 (80.7%)	27 (81.8%)	33 (80.5%)	0.693
AST IU/L	133.2 ± 73.4	144.5 ± 69.5	128.2 ± 59.3	140.6 ± 84.2	0.767
ALT IU/L	45.1 ± 23.5	44.4 ± 24.1	43.3 ± 20.1	47.7 ± 32.8	0.897
ALP IU/L	173.4 ± 63.1	193.9 ± 85.3	160.6 ± 62.9	188.2 ± 94.5	0.289
Hemoglobin g/Ll	9.7 ± 1.9	10.0 ± 2.1	9.5 ± 1.5	9.7 ± 1.7	0.648
Total WBC (x 10^9 /L)	11.6 ± 6.2	11.5 ± 5.8	12.7 ± 6.8	11.1 ± 6.2	0.727
Platelet Count (10^9 /L)	127.6 ± 91.1	176.0 ± 97.1	182.3 ± 130.9	163.6 ± 94.9	0.360
Albumin g/dL	2.8 ± 0.5	2.6 ± 0.5	2.8 ± 0.4	2.8 ± 0.5	0.478
Total Bilirubin, mg/dL	21.7 ± 10.0	19.1 ± 8.5	18.8 ± 8.0	17.6 ± 8.6	0.455
INR	2.1 ± 0.4	1.9 ± 0.5	2.1 ± 0.6	1.9 ± 0.4	0.511
Creatinine mg/dL	0.9 ± 0.3	0.8 ± 0.3	0.9 ± 0.4	0.8 ± 0.3	0.431
MELD Score	26.5 ± 3.8	24.6 ± 3.5	25.5 ± 3.5	24.5 ± 3.6	0.168
Maddrey Discriminant Score	66.3 ± 24.5	57.0 ± 24.3	62.8 ± 34.9	57.3 ± 22.7	0.523

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3569-C | INTERACTION OF CHRONIC AND HEAVY DRINKING, NUTRITION, AND PROGRESSION OF LIVER INJURY ENHANCES THE MORTALITY RISK IN ALCOHOL-ASSOCIATED HEPATITIS

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Background: Among the patients with alcohol use disorder (AUD), 20-30% eventually develop alcohol-associated liver disease (ALD). Alcohol-associated hepatitis (AH) is an acute inflammatory form of ALD with rapid progression of liver pathology resulting in high mortality. "Age-Bilirubin-INR-Creatinine" (ABIC) is a static mortality algorithm used to predict survival in AH. The role of chronic and heavy drinking and nutrition in the progression of liver injury and mortality is understudied. We evaluated the role of chronic and heavy drinking and clinical presentation in the risk of mortality in AH. **Methods:** 61 male and female adult patients were grouped by MELD (Model for End-Stage Liver Disease), as non-severe (nSAH as Gr.1, MELD < 20, $n = 26$), and severe (SAH as Gr.2, MELD ≥ 20, $n = 35$). Within each group, patients were sub-divided by ABIC grading into low (Unit < 6.71, $n = 10$ [Gr.1], $n = 6$ [Gr.2]), intermediate ($6.71 \geq$ unit $<$ 9, $n = 16$[Gr.1], $n = 20$[Gr.2]), and high (Unit > 9, $n = 9$ [Gr.2]) risk of 90-day mortality. Demographic, Nutritional status (CONUT [Controlling Nutritional Status] score), chronic (LTDH, Lifetime Drinking History [years]) and one-year drinking (AUDIT, Alcohol Use Disorders Identification Test), laboratory values (CMP [Complete Metabolic Panel], CBC [Complete Blood Count], etc.), and clinical presentation (MELD, Maddrey DF, CTP, Lille, AST:ALT [Aspartate transaminase: Alanine transaminase] ratio) were assessed. **Results:** Eight females and 18 males were in Gr.1, while Gr.2 had 13 females and 22 males. AH patients with increasingly worse prognosis (low survivability) corresponded to increasing age in both groups (Table 1). ABIC score showed positive correlation with LTDH ($r = 0.538$, $p = 0.004$); this effect was exhibited primarily in SAH ($r = 0.554$, $p = 0.011$).

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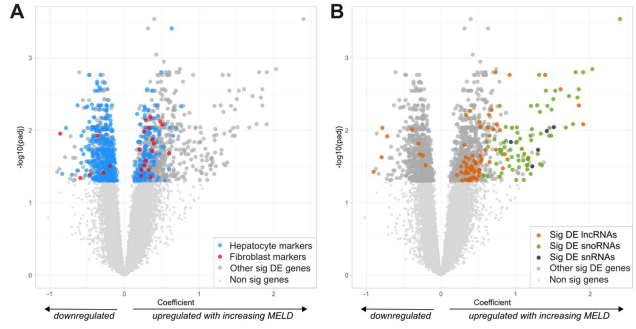
Stage Liver Disease (MELD) score was computed with DESeq2, adjusting for age and sex. Gene set enrichment analysis (GSEA) was computed with fgsea; cell type specific markers were annotated using the Liver Cell Atlas. Results were validated with cytochrome P450 2E1 (CYP2E1)- and alcohol dehydrogenase 1 (ADH1)-overexpressing VL-17A human hepatocyte cells treated with 100mM ethanol for 48h. A false discovery rate < 0.05 was considered significant. **Results:** We identified 1,613 genes associated with MELD. Hepatocyte markers were downregulated, while fibroblast markers were upregulated with worsening AH (Figure 1A). Acute inflammation was significantly enriched. Posttranscriptional regulation of gene expression was also enriched; splicing factors linked to liver dysfunction such as APOBEC1 complementation factor (A1CF) and muscle blind-like protein 3 (MBNL3) were downregulated with increasing MELD. Non-coding RNAs (ncRNAs) comprised 9% of DE genes; 49% were long non-coding RNAs (lncRNAs), 45% small nucleolar RNAs (snoRNAs) and 3% small nuclear RNAs (snRNAs). 94% of ncRNAs were upregulated with worsening AH and comprised 18% of all upregulated genes (Figure 1B). VL-17A cells treated with ethanol also showed downregulation of hepatocyte markers and splicing factors (e.g. albumin and MBNL3, respectively), as well as dysregulation of ncRNAs, including snoRNA upregulation. **Conclusion:** Loss of hepatocyte function in AH is characterised by dysregulation of ncRNAs and splicing factors with worsening disease severity. Our results indicate that epigenome and epitranscriptome modulation may be a promising therapeutic target in AH.



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3580-C | NOVEL CIRCULATING EXOSOMAL MIRNAS AND mRNA NETWORK OFFERS PATHOPHYSIOLOGIC INSIGHTS AND POTENTIAL FOR NEW BIOMARKER DISCOVERY AND THERAPEUTIC TARGETS IN PATIENTS WITH SEVERE ALCOHOL ASSOCIATED HEPATITIS (SAH)

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Background: Severe alcohol associated hepatitis (SAH) is associated with liver and multi-organ failure, resulting in a high demand for liver transplants and increased mortality. The pathogenesis of SAH involves various molecular mechanisms, including the dysregulation of microRNAs (miRs). Our hypothesis is that patients with SAH exhibit dysregulated circulating exosomal miRNAs (CE-miRs). To test this hypothesis, we examined the expression profiles and functions of hepatic miRNAs (H-miRs) and CE-miRs in SAH patients compared to healthy controls (HC). **Methods:** We extracted serum exosomes and isolated total RNA from exosomes and liver tissue. CE-miRs was analyzed using PartekFlow, while NanoString nCounter was employed for hepatic miRNAs (H-miRs). Potential target genes were identified using TargetScan and mirnet v2.0. Protein-protein interaction (PPI) networks were constructed using STRING database, and Cytoscape software was used to visualize hub genes. GSE28619 dataset data analysis were performed using ROSALIND® platform along with CE-miRs and H-miRs. **Results:** Our study included 25 patients, comprising 16 SAH patients (CE-miR n = 13, H-miR n = 3) and 9 HC (CE-miR n = 6, H-miR n = 3). In depth miR-seq data analysis revealed 78 differentially expressed CE-miRs (DE-CE-miRs). Among them, 50 were upregulated, while 28 were downregulated in SAH patients compared to HC. SAH liver tissue data exhibited 173 differentially expressed H-miRs (DE-H-miRs) compared to HC. Interestingly, among the upregulated DE-H-miRs, 11 CE-miRs were also upregulated in SAH patients. GO and KEGG analyses were performed to predict target genes for these 11 overlapping DE-miRs, and a PPI network analysis identified the top 50 hub genes. Using the GSE28619 dataset, we

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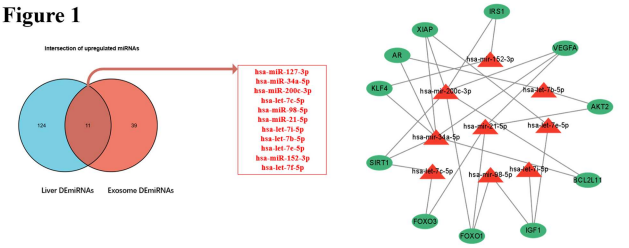
found that 12 out of the 50 identified hub genes were significantly downregulated in SAH patients compared to HC. These downregulated genes represent potential targets of the 9 upregulated CE-miRs (Figure 1). Moreover, these DE-miRs are associated with multiple signaling pathways related to cancer, including apoptosis, stress response and angiogenesis. **Conclusion:** The overlapping DE-miRs found in the liver and circulating exosomes are associated with severe alcohol-associated hepatitis (SAH). These findings indicate their potential as diagnostic and prognostic markers, as well as therapeutic targets for SAH. The upregulation of hsa-miR-152-3p may have cancer-protective effects and warrants further evaluation. **Keywords:** alcoholic hepatitis, miRNA, gene, exosome, expression profile, microarray analysis

Figure 1



•Exosomal miRNA-mRNA Network 9 exosomal miRNAs (red triangle) and 12 genes (green ellipse).

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3581-C | NOVEL PATTERNS AND SURVIVAL EFFECTS OF RE-ABSTINENCE AFTER HARMFUL ALCOHOL USE FOLLOWING EARLY LIVER TRANSPLANT FOR SEVERE ALCOHOL-ASSOCIATED HEPATITIS: AN ACCELERATE STUDY

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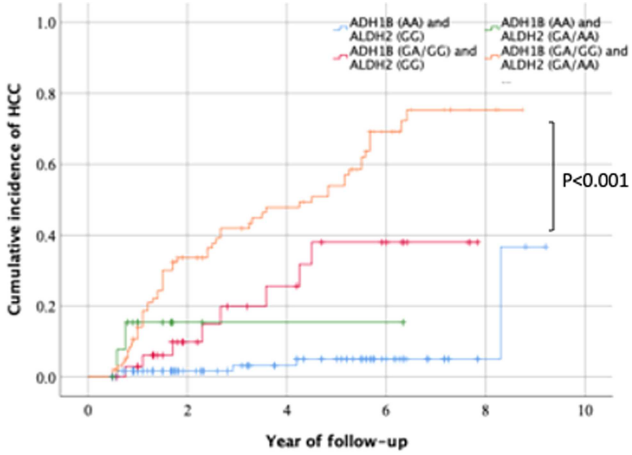
Background: Hepatocellular carcinoma (HCC) is the fifth most commonly occurring cancer and the second most common cause of cancer-related death worldwide. Heavy alcohol intake and hepatitis B virus (HBV) infection has been shown to increase the development of HCC. Our previous study showed that heavy alcohol intake with ALDH2 polymorphismpromoted the HCC in HBV-related cirrhosis. However, the role of heavy alcohol intake, ADH1B and ALDH2 rs671 polymorphism and HBV infection in HCC development remains unclear and needs to be explored. This study aims to investigate the correlation of heavy alcohol intake ADH1B and ALDH2 rs671 polymorphism, and HBV infection with HCC development in cirrhotic patients. **Methods:** This retrospective cohort study enrolled 698 cirrhotic patients with heavy alcoholism or/and HBV infection in E-Da Hospital, I-Shou University, and Kaohsiung Chang Gung Memorial Hospital, and General Cathay Hospital, Taiwan from January 2013 to December 2021. Data analyses were finalized on December 2022. The ADH1B and ALDH2 rs671 polymorphism was analysis. Heavy alcohol intake was defined as consuming more than 80 g of ethanol per day for at least 5 years. The primary endpoint was newly developed HCC. **Results:** This study included 290 patients with concomitant heavy alcoholism and HBV infection, 245 patients with HBV infection, and 207 patients with heavy alcoholism. Of 698 cirrhotic patients, 598 (85.4%) were men and the median (range) age was 47 (21-75) years. The 8-year cumulative incidences of HCC were significantly higher in cirrhotic patients with concomitant HBV infection and alcoholism than in those with HBV infection alone or alcoholism alone. The ADH1B genotype (GA/GG) significantly increased the risk of HCC [hazard ratio (HR) = 7.6; 95% CI, 4.1-13.8] compared with the ADH1B genotype (AA) in cirrhotic patients with concomitant HBV infection and alcoholism.Moreover, the ALDH2 rs671 genotype (GA/AA) significantly increased the risk of HCC (HR = 10.1; 95% CI, 4.6-22.2) compared with the ALDH2 rs671 genotype (GG) in cirrhotic patients with concomitant HBV infection and alcoholism. We combined the ADH1B and ALDH2 rs671 polymorphism to analyze the HCC development. The ADH1B genotype (GA/GG) and ALDH2 rs671 genotype (GA/AA) significantly increased the risk of HCC (HR = 16.3; 95% CI, 6.5-40.6) compared with the ADH1B genotype (AA) and ALDH2 rs671 genotype (GG) in cirrhotic patients with concomitant HBV infection and alcoholism.The cumulative incidences of HCC were significantly higher in patients with the ADH1B genotype (GA/GG) and ALDH2 rs671 genotype (GA/AA) than in those with the ADH1B genotype (AA) and ALDH2 rs671 genotype (GG) in cirrhotic patients with concomitant HBV infection and alcoholism. **Conclusion:** Heavy alcohol commutation with ADH1Band ALDH2 rs671 polymorphism significantly increased the risk of HCC development in HBV-related cirrhotic patients.



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3613-C | THE IMPACT OF OBESITY ON SEVERITY OF ACUTE ALCOHOLIC HEPATITIS

Marcus Allen Healey[1], Geetha Ramalingam[1], Yiwei Hang[1], Ekaterina Smirnova[2], Amon Asgharpour[3], Vaishali Patel[4], Hannah Lee[4], Velimir A. Luketic[2], Scott C. Matherly[4], Mohammad S. Siddiqui[4], Joel P. Wedd[4], Arun Sanyal[5] and Richard K. Sterling[4], (1)VCU Health, (2)Virginia Commonwealth University, Richmond, VA, (3)Virginia Commonwealth University, (4)Virginia Commonwealth University Health System, (5)Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA

Background: Obesity and alcohol use disorder (AUD) are leading causes of liver-related injury in the United States. Moreover, their effects appear synergistic in promoting steatohepatitis. However, the impact of body mass index (BMI), a surrogate marker for obesity, on severity of acute alcoholic hepatitis (AAH) is not well defined. Our aim is to compare the severity of AAH among hospitalized obese patients with BMI $\geq$ 30 kg/m2 to those with BMI < 30 kg/m2 from the same time

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period. **Methods:** Retrospective chart review of 199 patients hospitalized with AAH with BMI ≥ 30 kg/m2 from 2012-2019 was performed. For a control group, 419 patients hospitalized with AAH with BMI < 30 kg/m2 from the same time period were used. Age, race, ethnicity and gender were obtained for demographic characteristics. Laboratory parameters were obtained to include Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), total bilirubin (TB), international normalized ratio (INR), prothrombin time (PT), creatinine (Cr), and albumin. To define severity of AAH, both Model for End-Stage Liver Disease (MELD) and Maddrey's discriminant function (MDF) were computed. For control PT in the MDF calculation, 13.5 seconds was used. Steroid administration and thirty-day survival were compared, and odds ratio was computed for both variables. **Results:** Demographic and clinical characteristics of patients with BMI ≥ 30 kg/m2 and their controls are found in Table 1. Those with BMI ≥ 30 kg/m2 were found to have higher TB ($p = 0.002$), INR ($p < 0.001$), and creatinine ($p = 0.05$) which were statistically significant. Albumin was found to be significantly higher in those with BMI < 30 kg/m2 ($p = 0.001$). Patients with BMI ≥ 30 kg/m2 were found to have insignificantly lower AST and ALT ($p > .05$). MELD on admission ($p < 0.001$), MELD at discharge ($p = 0.026$) and MDF on admission ($p < 0.001$) appeared to be higher in those with BMI ≥ 30 kg/m2. While steroid administration was higher in the BMI ≥ 30 kg/m2 cohort, 30-d survival was not different between both groups. **Conclusion:** In our study, we found that when compared to those with BMI < 30 kg/m2, those with BMI ≥ 30 kg/m2 had more severe AAH (higher MELD and MDF). While steroid use was also higher in those with BMI ≥ 30 kg/m2, survival between these two groups was similar. Therefore, better methods to improve survival in AAH in this unique population are needed given the rising prevalence of both obesity and alcohol use disorder.

Contents	BMI < 30	BMI ≥ 30	Odds Ratio	Confidence interval	P-value
Number of subjects	419	199	-	-	-
Age in years	46.6 (11.6)	47.2 (9.96)		-1.240905, 2.316185	0.5528
Female/Male	178/241	84/115	-	-	-
Race (AA/W/unknown)	122/259/38	44/134/21	-	-	-
Ethnicity % non-Hispanic	93.55%	90.45%		-	-
Weight in kg	70.3 (12.9)	105 (20.9)		31.88801, 37.26886	$< 2.2\times10^{-16}$
AST U/L	275 (509)	219 (128)		-127.61510, 16.33164	0.1295
ALT U/L	102 (220)	82.7 (73.5)		-50.51628, 12.36346	0.2339
Total bilirubin mg/dl	10.0 (10.8)	13.1 (11.8)		1.147833, 5.032874	0.001899
Albumin g/dL	3.07 (0.752)	2.86 (0.637)		-0.3342085, 0.0916774	0.0006022
PT sec	18.3 (5.59)	20.8 (6.47)		1.466703, 3.457095	1.505e-06
INR	1.54 (0.628)	1.82 (0.733)		0.1618742, 0.3862266	2.016e-06
Creatinine mg/dl	0.982 (0.867)	1.13 (0.848)		-0.0007194, 0.2883079	0.051115
DF (using PT 13.5)	31.8 (32.8)	46.6 (34.8)		8.999861, 20.556905	7.707e-07
MELD (admission)	17.2 (10.3)	21.2 (9.29)		2.341234, 5.600644	2.312e-06
MELD (discharge)	20.1 (14.4)	22.7 (9.15)		0.308273, 4.882202	0.02621
FIB-4	12.2 (12.6)	13.5 (16.0)		-1.117781, 3.547988	0.3068
Thirty-day survival rate	91.16%	89.94%	1.05578	0.524336, 2.131582	1
Steroid administration	36.99%	51.75%	2.017809	1.324313, 3.088193	0.0008173

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Arun Sanyal – Durect: Stock – privately held company (individual stocks and stock options), No, No; GenFit: Stock – privately held company (individual stocks and stock options), No, No; Gilead: Consultant, No, No; Novartis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genetech: Consultant, No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Path-AI: Consultant, No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Histoindex: Consultant, No, No; Fibronest: Consultant, No, No; Hemoshear: Stock – privately held company (individual stocks and stock options), No, No; Hemoshear: Consultant, No, No; Inversago: Stock – privately held company (individual stocks and stock options), No, No; Biocellvia: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Eli Lilly: Consultant, No, No; Novo Nordisk: Consultant, No, No; Boehringer Ingelheim: Consultant, No, No; Astra Zeneca: Consultant, No, No; Boehringer Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Akero: Consultant, No, No; Intercept: Consultant, No, No; Fractyl: Consultant, No, No; Madrigal: Consultant, No, No; Northsea: Consultant, No, No; Takeda: Consultant, No, No; Regeneron: Consultant, No, No; Eli Lilly: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Alnylam: Consultant, No, No; Novo Nordisk: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Consultant, No, No; Glaxo Smith Kline: Consultant, No, No; Novartis: Consultant, No, No; Tern: Consultant, No, No; Inventiva: Consultant, No, No; Target Pharmasolutions: Consultant, No, No; Tiziana: Stock – privately held company (individual stocks and stock options), No, No; Uptodate: Royalties or patent beneficiary, No, No; Elsevier: Royalties or patent beneficiary, No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives

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The following people have nothing to disclose: Marcus Allen Healey, Geetha Ramalingam, Yiwei Hang, Ekaterina Smirnova, Vaishali Patel, Hannah Lee, Scott C. Matherly, Mohammad S. Siddiqui, Joel P. Wedd, Richard K. Sterling
Disclosure information not available at the time of publication: Velimir A. Luketic

3614-C | THE INFLUENCE OF PARENTAL ALCOHOL MISUSE AND LIVER DISEASE ON THE DEVELOPMENT OF ALCOHOL-ASSOCIATED HEPATITIS

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Background: While the genetic influences of alcohol use disorder (AUD) are well-documented, and probands with NAFLD cirrhosis are known to increase the risk of fibrosis in first-degree relatives, whether parental AUD and liver disease influence the risk of alcohol-associated hepatitis (AH) remains unclear. **Methods:** We examined the effects of parental AUD and liver disease-related death on the risk of AH development in offspring by combining the data from two observational cohorts. Both studies recruited AH cases and heavy drinking controls (HDC). Parental AUD and death due to liver disease were documented in the study entry; their associations with AH in the offspring were assessed with logistic regression models. **Results:** Data from 1,280 participants (864 subjects with AH and 416 HDC; 60% male for AH and 61.4% male for HDC) were analyzed. The mean ages of AH and HDC were comparable (45.4 for AH and 46.9 for HDC). Compared to HDC, AH cases were more likely to be white (84.4% vs. 77.4%), less likely to attend trade school/college/graduate programs (56.7% vs. 68.6%) and had higher BMI (29.7 vs. 28.5 kg/m^2). The cases on average drank less (189.3 vs. 304.7 total drinks, and 18.1 vs. 23.6 drinking days in the 30 days before study entry). 56% of AH cases and 61% of HDC had a parent with AUD; 7.8% of AH and 5.6% of HDC had a parent that had died of liver disease. Multivariate logistic regression showed that having a parent die of liver disease was associated with a significantly increased risk of AH after adjusting participants' characteristics and drinking behavior (adjusted OR = 2.2, 95% CI: [1.20, 4.14]). Table 1 shows correlates of AH. **Conclusion:** There may be a hereditary component to the development of AH, as indicated by liver disease-related death in a parent. The risk, however, appears to be independent of the influences of parental AUD and participants' own drinking behavior.

Table 1. Estimated effects of potential correlates for AH development

Effect	Estimated Odds ratios	95% Wald Confidence Limits	
Age at enrollment	0.985	0.973	0.997
Male sex	1.039	0.775	1.392
White	1.839	1.265	2.673
Trade School/College/Graduate-level education	0.492	0.361	0.671
BMI	1.022	1.002	1.042
Has a blood or natural father/mother been an alcoholic or problem drinker at ANY time in his/her life?	0.825	0.617	1.104
Did he/she die of liver disease? Yes	2.224	1.196	4.137
Indicate the total number of drinks for 30 days	0.998	0.997	0.999

Disclosures: Lauren D. Nephew – Delfi Diagnostics: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
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Arun Sanyal – Durect: Stock – privately held company (individual stocks and stock options), No, No; GenFit: Stock – privately held company (individual stocks and stock options), No, No; Gilead: Consultant, No, No; Novartis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genetech: Consultant, No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Path-AI: Consultant, No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Histoindex: Consultant, No, No; Fibronest: Consultant, No, No; Hemoshear: Stock – privately held company (individual stocks and stock options), No, No; Hemoshear: Consultant, No, No; Inversago: Stock – privately held company (individual stocks and stock options), No, No; Biocellvia: Consultant, No, No; Merck: Consultant, No, No; Pfizer: Consultant, No, No; Eli Lilly: Consultant, No, No; Novo Nordisk: Consultant, No, No; Boehringer Ingelheim: Consultant, No, No; Astra Zeneca: Consultant, No, No; Boehringer Ingelheim: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Akero: Consultant, No, No; Intercept: Consultant, No, No; Fractyl: Consultant, No, No; Madrigal: Consultant, No, No; Northsea: Consultant, No, No; Takeda: Consultant, No, No; Regeneron: Consultant, No, No; Eli Lilly: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Alnylam: Consultant, No, No; Novo Nordisk: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Roche: Consultant, No, No; Glaxo Smith Kline: Consultant, No, No; Novartis: Consultant, No, No; Tern: Consultant, No, No; Inventiva: Consultant, No, No; Target Pharmasolutions: Consultant, No, No; Tiziana: Stock – privately held company (individual stocks and stock options), No, No; Uptodate: Royalties or patent beneficiary, No, No; Elsevier: Royalties or patent beneficiary, No, No; Merck: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Bristol Myers Squibb: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Astra Zeneca: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No;
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3615-C | THE LANDSCAPE OF INPATIENT ADMISSIONS FOR ALCOHOLIC HEPATITIS IN THE ERA OF EARLY LIVER TRANSPLANTATION

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Background: Liver transplant (LT) is a recent option available in the United States (US) to treat those with severe, refractory alcoholic hepatitis (AH). We examined changes in clinical characteristics of patients admitted with AH and determined how hospital cost, length of stay (LOS), and mortality have changed as practice changes involving LT have shifted. **Methods:** Using the National Inpatient Sample, we performed a cross-sectional analysis of patients admitted with AH during the years 2016-2020 in the US. Differences in

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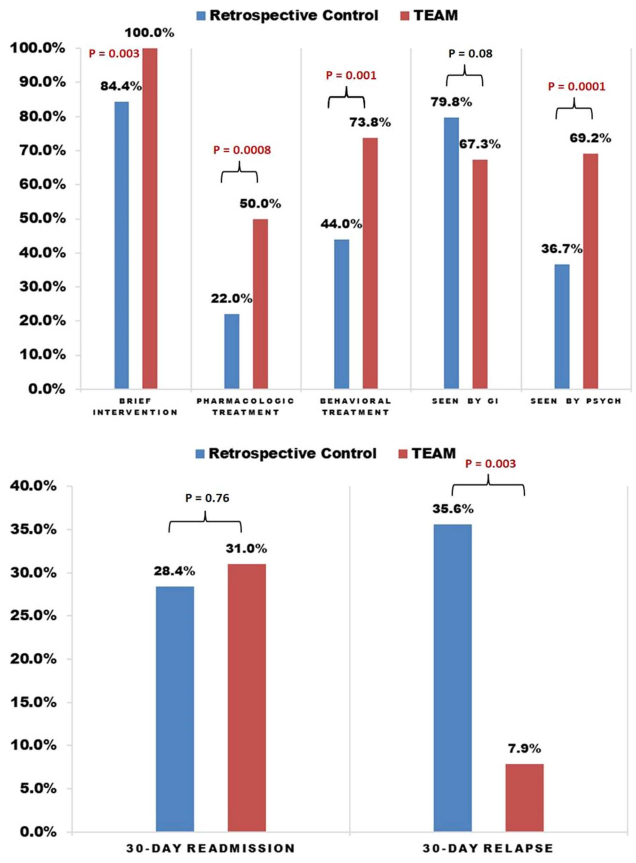

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3622-C | THE UTILITY OF LILLE SCORE IN PREDICTING 30-DAY SURVIVAL IN STEROID-TREATED ACUTE ALCOHOLIC HEPATITIS

Geetha Ramalingam[1], Marcus Allen Healey[1], Yiwei Hang[1], Ekaterina Smirnova[2], Amon Asgharpour[3], Vaishali Patel[3], Hannah Lee[3], Velimir A. Luketic[2], Scott C. Matherly[3], Mohammad S. Siddiqui[4], Joel P. Wedd[4], Arun Sanyal[5] and Richard K. Sterling[3], (1) VCU Health, (2)Virginia Commonwealth University, Richmond, VA, (3)Virginia Commonwealth University Health System, (4)Virginia Commonwealth University, (5)Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA

Background: In acute alcoholic hepatitis (AAH), steroids are considered if Discriminant Function (DF) is ≥ 32 or Model for End-Stage Liver Disease (MELD) is > 20 and no contraindications are present. However, not all patients respond favorably to steroids. The Lille score was created to assess futility of steroids in AAH. However, the utility of the Lille score and impact on 30-day (30-d) survival is needed. Our aim is to compare the utility of the Lille score on 30-d survival in those with AAH treated with steroids. **Methods:** Retrospective chart review of patients hospitalized with AAH who got steroids was performed (n = 272). Those with data to calculate Lille score < 0.45 on day 4 (n = 26) or 7 (n = 86) who continued steroids were compared to 83 patients with Lille scores ≥ 0.45 on day 4 (n = 18) or 7 (n = 65) who stopped steroids. Data on age, gender, race, ethnicity, BMI, and weight were gathered. Laboratory markers were obtained to include aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), internationalized normalized ratio (INR), prothrombin time (PT), albumin, and creatinine (Cr). DF on admission, and MELD upon admission and discharge was calculated. The primary outcome was 30-d survival. **Results:** Demographic and clinical characteristics of patients with Lille score < 0.45 and ≥ 0.45 are found in Table 1. Those with Lille Score < 0.45 were found to be younger (p = 0.001) with lower TB (p = 0.001), higher albumin (0.001), lower Cr(p = 0.001), and lower INR (p = 0.001). MELD and DF upon admission were found to be statistically significant, but MELD at discharge was not significant between cohorts (p = 0.104). In patients with Lille score < 0.45, survival was higher at 30-d (94.9% vs. 80.72%; p = 0.002). By comparison, a contemporary cohort hospitalized with AAH eligible but not receiving steroids (n = 206; 57% male, mean age 50, DF 47, MELD 24) had a 30-d survival of 87%. The sensitivity, specificity, PPV, and NPV of Lille score (< 0.45) to predict 30-d survival was 95%, 19%, 63%, and 73%, respectively. **Conclusion:** Our study shows that in AAH those with Lille score < 0.45 receiving steroids have improved 30-d survival (95%) that was better than those with Lille score ≥ 0.45 (81%). In those receiving steroids, Lille score on day 4 or 7 has excellent sensitivity but poor specificity to predict 30-d survival. Thus, while Lille score is sensitive to predict 30-d survival, its poor specificity implies a need for better scores to determine outcomes in this population.

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S.No	Contents	Lille score less than 0.45	Lille score greater/equal to 0.45	Odds ratio	Confidence interval	P-value
1.	Number of subjects	118	83		-	-
2.	Age in years	43.0(10.2)	49.2 (11.6)		3.117089, 9.357692	0.0001175
3.	Female/Male	59/59	44/39		-	-
4.	Race (AA/W/unknown)	19/85/14	12/64/7		-	-
5.	Ethnicity % non-Hispanic	88.9%	95.18%		-	-
6.	Weight in kg	82.8(22.3)	88.2(27.0)		-1.731753, 12.499039	0.137
7.	BMI kg/m2	28.6(6.81)	32.0(19.8)		-0.4364208, 7.3287753	0.08161
8.	AST U/L	226(200)	199(102)		-74.51792, 19.50076	0.2499
9.	ALT U/L	60.2(51.7)	58.9(35.6)		-14.19588, 11.64453	0.8458
10.	Total bilirubin mg/dl	16.2(10.4)	21.7(11.9)		2.314396, 8.702225	0.0008332
11.	Albumin g/dL	2.79(0.532)	2.51(0.494)		-0.4220430, -0.133787	0.0001933
12.	PT sec	20.9(5.25)	24.4(6.26)		1.836214, 5.155209	5.218×10^{-05}
13.	INR	1.81(0.588)	2.21(0.741)		0.2014558, 0.5857783	8.579×10^{-05}
14.	Creatinine mg/dl	0.927(0.584)	1.32(0.934)		0.1782097,0.6009489	0.0003545
15.	DF (using PT 13.5)	50.2(26.9)	71.7(31.8)		13.14245, 30.03465	1.218×10^{-06}
16.	MELD (admission)	22.1(7.03)	28.1(7.24)		3.939478, 7.985237	2.818×10^{-08}
17.	MELD (discharge)	24.8(19.7)	28.6(6.67)		-0.790503, 8.380713	0.1042
18.	FIB-4	12.3(15.0)	13.8(12.0)		-2.267706, 5.244427	0.4355
19.	Thirty-day survival rate	94.91%	80.72%	0.2260463	0.06895955, 0.64489193	0.002298

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3623-C | TIMING OF INITIATION OF CORTICOSTEROIDS IN SEVERE ALCOHOL-ASSOCIATED HEPATITIS HAS NO IMPACT ON SURVIVAL

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Background: Although corticosteroids are recommended for the treatment of severe alcohol-associated

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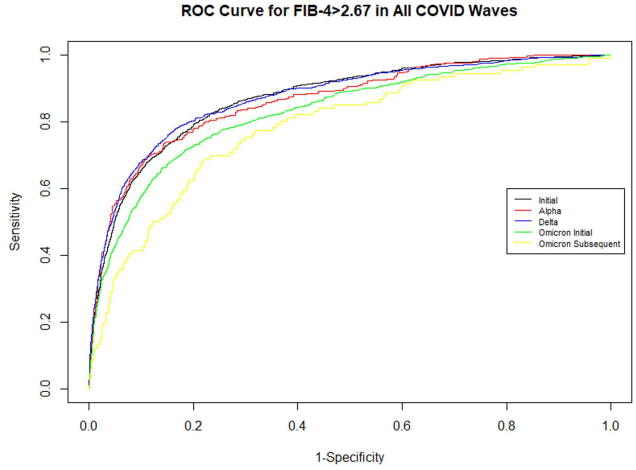
3736-C | FIBROSIS-4 (FIB-4) INDEX AS A PREDICTOR FOR MECHANICAL VENTILATION AND 30-DAY MORTALITY ACROSS COVID-19 VARIANTS

Priyanka Parajuli[1], Roy Sabo[2], Rasha Alsaadawi[2], Amanda Robinson[3], Evan French[1] and Richard K. Sterling[4], (1)Virginia Commonwealth University, (2) Virginia Commonwealth University, Department of Biostatistics, Richmond, VA, (3)Virginia Commonwealth University, C. Kenneth and Dianne Wright Center for Clinical and Translational Research, Richmond, VA, (4) Virginia Commonwealth University Health System

Background: The evolution of the severe acute respiratory syndrome coronavirus has led to new variants of concern that vary in transmissibility, severity or change in clinical presentation. Recent studies of the Omicron variant have shown reduced odds of hospitalization with Omicron vs. the prior Delta variant. The Fibrosis-4 (FIB-4) index, a simple index that includes age, liver enzymes, and platelet count has been studied as a risk-stratification tool for front-line health care professionals to quickly identify patients at a risk of requiring mechanical ventilation (MV) from Coronavirus disease 2019 (COVID-19) due to its high negative predictive value (NPV). The main objective was to determine if FIB-4 can predict MV requirements and 30-day mortality from COVID-19 across variants including Alpha, Delta, and Omicron. **Methods:** This was a retrospective cohort analysis of 232,364 COVID-19 positive patients between April 27, 2020 and June 25, 2022 within the National COVID Cohort Collaborative database. Simple logistic regression (SLR) and multiple logistic regression (MLR) models were utilized to investigate potential bivariate associations between MV use and various patient characteristics including age, liver enzymes, platelet counts, sex, and comorbid conditions. MLR models were fit between categorical FIB-4 covariates (FIB-4 > 2.67, > 3.04, > 3.25) and MV use for each COVID variant. The sensitivity, specificity, positive predictive value (PPV), NPV, and the area under the receiver operating characteristic (AUROC) curve were calculated. The primary outcome was association of FIB-4 and need for MV. Secondary measures included the association of FIB-4 with 30-day mortality. **Results:** Of the cohort, 12,207 were hospitalized during the Alpha wave, 38,187 during the Delta wave, 34,871 during the Omicron-initial wave, and 6,915 during the Omicron-subsequent wave. A FIB-4 > 2.67 had 1.8 times higher odds ratio (OR) of requiring MV across all variants of COVID-19 (OR 1.81; 95% CI: [1.76,1.86]). A FIB-4 > 3.04 and a FIB-4 > 3.25 also had a 1.8x higher odds overall across all variants. The AUROC curve showed a high sensitivity ranging from 0.78 to 0.80 for the initial variant, 0.74 for Alpha, 0.76-0.78 for Delta, 0.70-0.71 for Omicron, and 0.67-0.71 for the subsequent Omicron variant. The specificity ranged from 0.83 to 0.84 across all variants. The NPV ranged from 0.96 to 0.97 overall across all variants. Simple logistic survival regression (SR) and multiple logistic survival regression (SR) modeling for FIB-4 as a continuous variable showed an increased odds of 30-day mortality (OR 1.21; 95% CI: [1.20, 1.21]) throughout all waves without significant variability between variants. **Conclusion:** The FIB-4 index was consistently associated with both increased utilization of MV and 30-day mortality among COVID-19 patients across all waves in both adjusted and unadjusted models, solidifying its utility amongst COVID-19 patients.



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♦ 3737-C | GEOGRAPHIC OPPORTUNITIES FOR GROWTH IN THE TRANSPLANT HEPATOLOGY TRAINING WORKFORCE★

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Background: The US hepatology workforce is predicted to shrink in the coming decade, with this differential regional impact. As a result, it is important that the hepatology community identify opportunities for physician growth, especially in resource limited settings, such as transplant hepatology (TH) fellowship programs. **Methods:** We reviewed the Scientific Registry of Transplant Recipients data for programs that performed ≥ 20 liver transplants (LTs) per year (the minimum volume required to have a TH fellowship [ACGME 2022]). We identified if these programs had TH fellowships by searching the center websites as well as the AASLD TH application portal. We compared this

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NAFLD risk stratification, with more frequent use among primary care clinicians as compared to sub-specialities. Barriers to screening for NAFLD include competing patient issues (75%), lack of confidence in screening (63%), limited time during clinic visit (59%) and the perceived lack of effective therapies (34%). Half the clinicians (55%) felt that they did not have enough resources to address NAFLD and a quarter felt that patients with suspected NAFLD should be referred to gastroenterology. Thirteen survey respondents participated in qualitative interviews (9 primary care, 2 geriatrics, 2 endocrinology). The following themes about knowledge and attitude about NAFLD emerged: clinicians were concerned about under-recognition of NAFLD; they perceived that NAFLD had fewer complications than other liver diseases; across specialties, they believe screening should occur in primary care; they acknowledge that currently screening and risk stratification for NAFLD is not normative or encouraged. In addition to barriers identified in the survey, clinicians felt that availability of easy to use and unobtrusive EHR tools would facilitate NAFLD diagnosis and risk stratification. **Conclusion:** Our findings suggest implementation strategies to improve clinician knowledge and to deploy well-defined easy-to-use EHR tools, especially in primary care clinics, can bolter NAFLD screening and risk stratification practices.

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3762-C | PRIMARY CARE SCREENING FOR NAFLD AMONG PEOPLE WITH HIV: A REAL-WORLD PROVIDER SURVEY

Jennifer C. Price[1], Kyoko Hirose[1], Naga P. Chalasani[2], Holly Crandall[3], Sonya Heath[4], Rohit Loomba[5], Susanna Naggie[6], Richard K. Sterling[7], Mark S Sulkowski[8], Laura Wilson[9] and Jordan E. Lake[10], (1) University of California, San Francisco, (2)Indiana University Medical Center, Indianapolis, IN, (3)Indiana University, (4)University of Alabama at Birmingham, (5) University of California, San Diego, San Diego, CA, (6) Duke Clinical Research Institute, Durham, NC, (7) Virginia Commonwealth University Health System, (8) Johns Hopkins University School of Medicine, Division of Infectious Diseases, (9)Johns Hopkins School of Public Health, (10)Division of Infectious Diseases, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA

Background: Nonalcoholic fatty liver disease (NAFLD) is highly prevalent in people with HIV (PWH) and increases the risk of hepatic fibrosis and hepatocellular carcinoma. To better inform recommendations for NAFLD screening among PWH, we surveyed HIV providers on their NAFLD screening patterns and management needs. **Methods:** An online survey was sent to American Academy of HIV Medicine (AAHIVM) member and non-member HIV providers 3 times over 6 weeks Jan-Feb 2023. The survey was restricted to physicians and advanced practice providers working in the US, Puerto Rico, and US Virgin Islands (n = 2,753). Questions assessed NAFLD screening and referral practices, barriers to screening, and attitudes toward support tools. **Results:** Of respondents (n = 215, 8% response rate), 60% were physicians, 27% nurse practitioners, 12% physician assistants, and most (52%) had been in practice for > 10 years. Sixty-five percent reported screening for NAFLD in PWH, with 28% routinely screening all patients (Figure). The most cited reasons for screening were persistently elevated liver enzymes, metabolic syndrome, obesity, and pre-diabetes/diabetes. Liver enzymes (90%) and abdominal ultrasound (71%) were the most common modalities used for NAFLD screening, with vibration controlled transient elastography (VCTE, 33%) and MRI (3%) less commonly used. The majority of respondents refer patients to hepatology if work-up suggests another co-existing liver disease or abdominal imaging suggests cirrhosis, with the primary goals of referral being additional diagnostic testing (60%) or specific treatments (75%). The most common barriers to NAFLD screening were not feeling sure of what tests to order (28%) and not knowing when there is enough data to make the diagnosis (29%). A low proportion reported screening being a low priority (17%), not having enough time to screen (7%) or not having access to hepatology referrals (7%) as barriers. When asked what tools would help in diagnosing and managing NAFLD in PWH, the majority were interested in society guidelines (73%) and NAFLD education for patients (57%) and providers (55%). A high proportion also reported interest in electronic medical record tools to assist NAFLD work-up and referral. **Conclusion:** Two-thirds of survey respondents reported screening for NAFLD in at least some of their patients, and the most common reason for hepatology referral was for treatment options. The majority believed society guidelines and increased education would help with NAFLD diagnosis and

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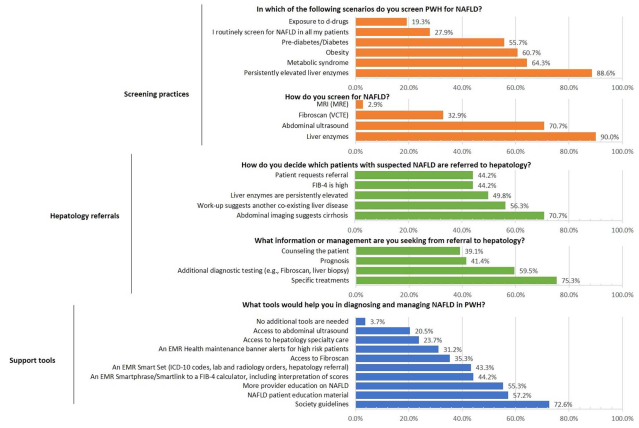
management. Our findings support the development of NAFLD clinical practice guidelines for HIV providers and the inclusion of PWH in clinical trials of novel agents.



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3763-C | PROTOCOLIZED HEPATITIS B VACCINATION TO INCREASE VACCINATION RATES AND IDENTIFY BARRIERS TO CARE IN PATIENTS UNDER LIVER TRANSPLANT EVALUATION

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Background: Shortage of appropriate donor livers is an obstacle for liver transplantation in the United States, therefore there is significant interest in expanding the pool of potential donors. Use of donors that are hepatitis B (HBV) positive is a potential source of donors, however there is risk of causing chronic HBV infection in the recipient. This risk can be reduced significantly if the recipient is immune to HBV. Nationally only about 25% of adults show serologic evidence of HBV immunity whereas at our center about 52% of liver transplants candidates were immune at the time of evaluation. Although it is recommended for all liver transplant candidates to be vaccinated if they are not immune to HBV, there are significant logistic and financial obstacles to completing the vaccine series. At our center historically only 7.14% of non-immune patients evaluated for liver transplant completed the vaccine series. Therefore we sought to identify barriers to vaccination at our center and create workflow to improve our vaccination rate **Methods:** Under the historic protocol at our center patients were responsible for obtaining required vaccines independently. Under the new protocol, HBV serology was obtained prior to transplant evaluation. This was followed by financial screening for vaccine coverage and patients scheduled during their transplant evaluation if they were not HBV immune. The vaccines were administered during their pharmacy consultation. Vaccine completion was evaluated and causes for failure to vaccinate recorded. **Results:** During this period vaccination rates increased from 7.14% prior to implementation of a standardized HBV vaccination protocol to 32% after implementation. The primary barrier to vaccination was inability to obtain financial/insurance authorization for vaccination either in specialty (hepatology) clinic or through the pharmacy and was the reason for non-vaccination in 73% of candidates. Of the patients who were denied coverage for vaccination, 12/14 had Medicare as their primary insurance and two had Medicaid. None of the 12 patients with private insurance were denied coverage for HBV vaccination. **Conclusion:** Protocolized HBV vaccination can improve immunity among liver transplant candidates but despite this, significant barriers remain to universal vaccination. The primary barrier at our center is lack of insurance authorization and

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◆ 3791-C | Development and Validation of Prognostic Model to Predict Risk of Sepsis Among Patients With Cirrhosis

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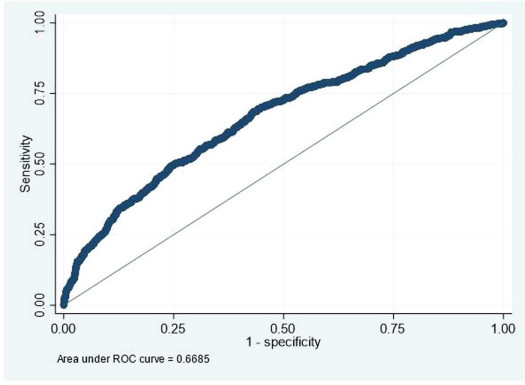
Background: Patients with cirrhosis are at risk for developing sepsis which is associated with high mortality. Prognostic tools estimating a patient's risk of sepsis could inform management. The aims of this study were to investigate predictors of sepsis and to develop a prognostic model among patients with cirrhosis. **Methods:** A total of 4045 adult patients with cirrhosis were included in the analysis from a retrospective single-center cohort. The demographic, clinical, and laboratory data were collected at baseline. A simplified prognostic model was developed using multiple logistic regression after identifying significant predictors of 30-day sepsis risk. **Results:** The 30-day overall risk of sepsis was 12.2%. Baseline characteristics of study population are summarized in table 1. Age, diabetes, hypertension, white blood cell count (WBC), hemoglobin (Hgb), creatinine, total bilirubin, and albumin were identified as independent risk factors for sepsis in cirrhosis patients. A new logistic model was developed from independent prognostic factors using multivariate analysis and calculated using the equation (0.97 x age) + (1.3 x diabetes) + (1.3 x hypertension) + WBC + (0.88 x Hgb) + (1.1 x creatinine) + (0.97 x total bilirubin) + (0.70 x albumin). This model's area under the receiver operating characteristics (AUROC) was 0.67. Validation analysis showed that the AUROC values were consistent (0.67) (figure 1). **Conclusion:** Our new simplified model can be used to predict the 30-day risk of sepsis among patients with cirrhosis which can lead to early identification of high-risk patients who might benefit from greater attention and early targeted interventions thus improving survival and patient care.

Table 1. Baseline characteristics of overall study population, and patients with and without sepsis.

	Overall (N = 4,045)	No sepsis (N = 3,550)	Developed sepsis (N = 495)	P-value
Age, median (IQR), y	54 (48-60)	55 (48-61)	53 (46-60)	0.000
Male (n (%))	2,187 (54.1)	1,927 (54.3)	260 (52.5)	0.463
Race/Ethnicity (n (%))				0.000
White, non-Hispanic	2,264 (64.1)	2,011 (65.3)	253 (55.6)	
Black, non-Hispanic	1,072 (30.3)	890 (28.9)	182 (40.0)	
Hispanic	47 (1.3)	45 (1.5)	2 (0.44)	
Other+	152 (4.3)	134 (4.4)	18 (4.0)	
BMI, median (IQR), Kg/m2 ++	29.2 (25.1-34.4)	29.3 (25.2-34.5)	28.4 (24.1-33.3)	0.770
Diabetes mellitus (n (%))	920 (22.7)	767 (21.6)	153 (30.9)	0.000
Hypertension (n (%))	1,556 (38.5)	1,323 (37.3)	233 (47.1)	0.000
Cardiac disease (n (%))				
Prior MI	100 (2.5)	74 (2.1)	26 (5.3)	0.000
CHF	356 (8.8)	270 (7.6)	86 (17.4)	0.000
Smoking (n (%)) *				0.101
Non-smoker	1,041 (25.7)	904 (58.5)	137 (53.1)	
Smoker	761 (18.8)	640 (41.5)	121 (46.9)	
Other cancers (n (%))	585 (14.5)	491 (13.8)	94 (19.0)	0.002
Etiology of chronic liver disease (n (%))				
NAFLD	2,707 (66.9)	2,383 (67.1)	324 (65.5)	0.459
Alcoholic liver disease	578 (14.3)	491 (13.8)	87 (17.6)	0.026
Viral hepatitis	2,075 (51.3)	1,849 (52.1)	226 (45.7)	0.007
Laboratory Results, (mean±SD)				
White blood cell count (x10^9/L) **	7.0 (4.0)	6.9 (3.6)	7.7 (6.0)	0.000
Hemoglobin (g/dL) **	13.1 (2.4)	13.0 (2.3)	11.9 (2.5)	0.000
Platelet Count (x10^9/L) **	177.9 (97.1)	177.9 (95.6)	177.8 (107.1)	0.987
Creatinine (mg/dL) **	0.82 (1.2)	1.1 (1.1)	1.4 (1.8)	0.000
Total cholesterol (mg/dl) **	162.3 (59.8)	163.0 (59.2)	159.3 (62.8)	0.411
LDL (mg/dl) **	93.1 (42.3)	94.2 (42.7)	88.1 (39.7)	0.081
Triglycerides (mg/dl) **	148.7 (124.2)	149.5 (127.1)	145.2 (109.9)	0.669
ALT (U/L) **	81.9 (169.9)	80.9 (124.7)	89.1 (350.3)	0.323
AST (U/L) **	89.2 (137.5)	87.4 (116.7)	102.2 (236.0)	0.027
ALP (U/L) **	149.8 (151.6)	146.2 (145.6)	174.7 (186.6)	0.000
Bilirubin, total (mg/dL) **	1.9 (3.9)	1.9 (4.0)	2.3 (3.8)	0.020
INR **	1.2 (0.39)	1.2 (0.4)	1.3 (0.4)	0.000
Albumin (g/dL) **	3.7 (0.73)	3.7 (0.7)	3.4 (0.8)	0.000
Hemoglobin A1c (%) **	6.6 (1.8)	6.6 (1.7)	6.8 (2.3)	0.223
FIB-4 score **	4.6 (5.5)	4.5 (5.3)	5.1 (6.6)	0.015
MELD score **	20.5 (9.8)	20.2 (9.7)	22.6 (10.2)	0.000
MELD score (n (%))				0.000
20-29	588 (18.3)	486 (17.3)	102 (25.4)	
30-39	150 (4.7)	118 (4.2)	32 (8.0)	
≥ 40	156 (4.9)	122 (4.3)	34 (8.5)	
FIB-4 score (n (%))				0.551
1.45-3.25	1,158 (30.9)	1,021 (31.1)	137 (29.4)	
>3.25	1,762 (47.0)	1,532 (46.7)	230 (49.4)	

+Other category included Asian, American Indian-Alaskan or other.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BMI, body mass index; CHF, congestive heart failure; FIB-4, fibrosis-4; INR, international normalized ratio; IQR, interquartile range; LDL, low density lipoprotein; MELD, model for end-stage liver disease; MI, myocardial infarction; SD, standard deviation.
++Missing values in 1,108 patients.
*Missing data in 2,243 patients.
**Missing values in 231, 226, 227, 386, 2,789, 3,027, 2,969, 255, 247, 251, 264, 385, 256, 2,985, 296, 599 patients, respectively.

Figure 1. ROC curve of prognostic model for predicting 30-day risk of sepsis in patients with cirrhosis.



Cutpoint	Sensitivity	Specificity	Correctly classified	LR+	LR-
(>= 0.5)	76.51%	23.97%	30.42%	1.0063	0.9801

Disclosures: Arun Sanyal – Durect: Stock – privately held company (individual stocks and stock options), No, No; GenFit: Stock – privately held company (individual stocks and stock options), No, No; Gilead: Consultant, No, No; Novartis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genetech: Consultant, No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Path-AI: Consultant, No,

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The following people have nothing to disclose: Somaya Albhaisi, Ekaterina Smirnova

3792-C | EFFECT OF DIFFERENT RADIOLOGIC MODALITIES FOR SURVEILLANCE OF HEPATOCELLULAR CARCINOMA ON SURVIVAL OF HIGH RISK CIRRHOTIC PATIENTS.

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Background: American Association for the Study of Liver Diseases (AASLD) recommends that patients with high risk of developing hepatocellular carcinoma (HCC) undergo regular surveillance with ultrasonography (US) every 6 months with or without Alpha-feto protein (AFP). However, compared to cross-sectional imaging modalities -Computed tomography (CT) and Magnetic resonance imaging (MRI) - US has lower efficacy for detection of early HCC. To our knowledge, there are no studies evaluating the overall survival and receipt of curative treatment for patients who received surveillance using the different imaging modalities. **Methods:** We retrospectively reviewed all patients who were diagnosed with HCC at Baylor Saint Luke's Medical Center Hospital between January 2011 and June 2021. Patients who underwent regular surveillance were identified. Data retrieved from electronic medical records and radiology reports included demographic and laboratory features, surveillance modality, tumour characteristics, treatments received and survival data. We estimated survival using the Kaplan-Meier method and compared the different modalities using the Log Rank test. We used univariate and multivariate Cox model to evaluate factors affecting survival. **Results:** A total of 183 patients developed HCC while on biannual surveillance program (115 with MRI, 34 with CT and 34 with US). Patients were similar regarding with respect to age, sex, comorbid diseases. However, our cohort shoed statistically significant differences regarding race and ethnicity, with more African American and Hispanic population undergoing surveillance with US. Moreover, Race and ethnicity were associated with lower survival rates. The initial survival analysis showed that compared to other modalities MRI had statistically significant association with longer survival (p-value = 0.034). However, cox-multivariate regression model with adjustment for race, ethnicity, MELD score and total tumor size at time of diagnosis shows that surveillance modality has no statistically significant association with

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[95%CI: 0.10-0.76]), LR- (1.92 [95%CI: 1.12-2.73]), and accuracy (35% [95%CI: 25-46%]). There was similar diagnostic accuracy of the 90-day SQ between hepatology attendings and trainees/APPs (47% vs. 46%) and IM attendings and trainees/APPs (37% vs. 36%) (Table). **Conclusion:** The surprise question's accuracy was poor in predicting 90-day mortality of patients with DC based on hepatologist or IM clinician response. This underscores the difficulty with prognostication in the context of DC.

Table. Performance of Surprise Question (SQ) in Predicting 90-Day Mortality of Patients with Decompensated Cirrhosis

	Hepatology Attendings n = 30	Hepatology Trainees/APPs n = 24	IM Attendings n = 68	IM Trainees/APPs n = 42
SQ+ (n, %)†	1 (9.1)	1 (12.5)	4 (22.2)	2 (20)
SQ- (n, %)†	10 (90.9)	7 (87.5)	14 (77.8)	8 (80)
Total death (n, %)*	11 (36.7)	8 (33.3)	18 (26.5)	10 (23.8)
Total sample (n, %)	30 (100)	24 (100)	68 (100)	42 (100)
Sensitivity (95% CI)	9 (0, 26)	13 (0, 35)	22 (3, 41)	20 (0, 45)
Specificity (95% CI)	68 (48, 89)	63 (39, 86)	42 (28, 56)	41 (24, 58)
PPV (95% CI)	14 (0, 40)	14 (0, 40)	12 (1, 23)	10 (0, 22)
NPV (95% CI)	57 (36, 77)	59 (35, 82)	60 (44, 76)	62 (41, 83)
LR+ (95% CI)	0.29 (-0.28, 0.86)	0.33 (-0.31, 0.98)	0.38 (0.04, 0.73)	0.34 (-0.09, 0.77)
LR- (95% CI)	1.33 (0.85, 1.81)	1.40 (0.75, 2.05)	1.85 (1.10, 2.61)	1.97 (0.94, 3.00)
Accuracy (95%CI)	47 (29, 65)	46 (26, 66)	37 (25, 48)	36 (21, 50)

†: denominator is total death (i.e. number of clinicians who answered SQ+ or SQ- for patients who died within 90 days)
*: denominator is total sample.
APP: Advanced Practice Provider; IM: Internal Medicine; PPV: Positive predictive value; NPV: Negative predictive value; LR+: Positive likelihood ratio; LR-: Negative likelihood ratio; CI: Confidence interval.

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♦ 3806-C | PREDICTING LIVER-RELATED OUTCOMES IN PATIENTS WITH CIRRHOSIS: THE PROGNOSTIC VALUE OF CLINICAL FACTORS AND NONINVASIVE TESTS

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Background: Patients with cirrhosis are at risk for developing complications which are associated with high mortality. Prognostic tools estimating a patient's risk of adverse liver outcomes based on cirrhosis etiology could inform disease management. The aims of our study were to investigate predictors of adverse liver outcomes and to develop simplified prognostic models by disease etiology among patients with cirrhosis. **Methods:** Six prognostic models were developed using proportional hazards regression, classified by cirrhosis etiology, after identifying meaningful predictors of 5-year risk of ascites, hepatic encephalopathy (HE), and variceal bleeding (VB) among patients with cirrhosis due to nonalcoholic steatohepatitis (NASH) or viral hepatitis (table 2). The predictors for each model were selected via LASSO regression. **Results:** A total of 4045 adult patients with cirrhosis were included in the analysis from a single U.S. center retrospective cohort. The 5-year rates were 31.6%, 22.9%, and 30.7% for ascites, HE, and VB, respectively. Baseline characteristics of study population are summarized in table 1. Multivariable analyses showed that independent predictors in cirrhosis due to NASH and viral hepatitis were: (a) ascites: albumin and international normalized ratio (INR); (b) HE: albumin, INR, total bilirubin, platelet count; (c) VB: albumin, platelet count, hemoglobin. No variables were significantly associated with outcomes in patients with alcohol-associated liver disease. Validation analyses based on 30-day risk showed that these models were reasonably predictive (table 3). **Conclusion:** Our new, simplified models accurately and consistently predicted 5-year risk of ascites, HE, and VB among patients with cirrhosis due to NASH or viral hepatitis using simple routinely available variables measured at baseline. These models could be employed to identify high-risk patients who might benefit from greater attention and more aggressive treatments.
Disclosures: Arun Sanyal – Durect: Stock – privately held company (individual stocks and stock options), No, No; GenFit: Stock – privately held company (individual stocks and stock options), No, No; Gilead: Consultant, No, No; Novartis: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Genetech: Consultant, No, No; Madrigal: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Path-AI: Consultant, No, No; Intercept: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Pfizer: Grant/Research Support (research funding from ineligible companies should be disclosed by the principal or named investigator even if that individual's institution receives the research grant and manages the funds), No, No; Histoindex: Consultant, No, No; Fibronest: Consultant, No, No; Hemoshear: Stock – privately held company (individual stocks and stock options), No, No; Hemoshear: Consultant, No, No; Inversago: Stock – privately

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The following people have nothing to disclose: Somaya Albhaisi, Rasha Alsaadawi, Amanda Robinson, Roy Sabo

3807-C | PREVALENCE AND PREDICTORS OF LIVER FIBROSIS IN A HOUSTON COMMUNITY CLINIC

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Background: Liver fibrosis may lead to hepatocellular carcinoma (HCC). Hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, metabolic syndrome, and alcohol use disorder (AUD) are risk factors for fibrosis. Early screening for fibrosis using serum biomarkers in community settings is not well established. **Methods:** Adult patients at the HOPE Clinic, a federally qualified health care center in Houston, were enrolled from January 2021 through May 2023 and surveyed about risk factors for liver fibrosis. We measured vital signs and waist circumference, calculated body mass index (BMI), and performed blood testing. We defined chronic HBV infection as positivity for hepatitis B surface antigen; chronic HCV infection as detectable HCV RNA; metabolic syndrome as the presence of at least 3 of 4 conditions: hyperglycemia, hypertension, dyslipidemia, and obesity; and AUD as an AUDIT-C score of ≥ 4 for men and ≥ 3 for women. Transient elastography was performed to assess for fibrosis, with scores ≥ 8 kPa indicating $\geq$F2 fibrosis. Serum biomarkers of fibrosis were defined as Fibrosis-4 (FIB-4) score ≥ 2.67 (based on ALT, AST, platelets, age); NAFLD Fibrosis Score (NFS) ≥ 0.675 (based on ALT, AST, platelets, albumin, age, BMI, diabetes); and Fatty Liver Index (FLI) ≥ 30 (based on triglycerides, gamma-glutamyl transferase, waist circumference, BMI). We described the prevalence of fibrosis risk factors and tested the associations of risk factors and serum biomarkers with $\geq$F2 fibrosis using Fisher's exact test. Logistic regression was used to model the outcome of $\geq$F2 fibrosis. **Results:** We enrolled 977 patients, 409 men (42%) and 568 women (58%). The median age was 48 years (IQR = 22). A total of 483 patients (50%) were White, 252 (27%) were Asian, and 210 (22%) were Black. Among all patients, 394 (41%) were Hispanic. Forty-three percent of patients (n = 416) had BMI ≥ 30. Six percent of patients (57/944) had chronic HBV infection, $< 1\%$ (1/939) had chronic HCV infection, 48% (440/912) had metabolic syndrome, and 13% (125/971) had AUD. Of 891 patients who completed transient elastography, 86 (10%) had $\geq$F2 fibrosis. Among patients with metabolic syndrome, FIB-4 score ≥ 2.67 (OR 26.2, 95% CI 5.3-129.7) and NFS ≥ 0.675 (OR 8.9, 95% CI 2.3-34.3) were predictive of $\geq$F2 fibrosis, but FLI ≥ 30 (OR 4.5, 95% CI 0.7-27.6) was not. The receiver operating characteristic curve for

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The following people have nothing to disclose: Katherine M. Cooper
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3812-C | STIGMA IS A PREDICTOR OF IMPAIRMENT OF HEALTH RELATED QUALITY OF LIFE AMONG PATIENTS WITH NAFLD

Zobair M. Younossi[1], Yusuf Yilmaz[2], Jian-Gao Fan[3], Ming-Hua Zheng[4], Khalid Aida Alswat[5], Saleh A Alqahtani[6], Mohamed El-Kassas[7], Laurent Castera[8], Jesús Funuyet-Salas[9], Manuel Romero-Gómez[10], Vincent Wai-Sun Wong[11], Shira Zelber-Sagi[12], Sombat Treeprasertsuk[13], Alina M. Allen[14], Hirokazu Takahashi[15], Takumi Kawaguchi[16], Sven Francque[17], Marlen Ivon Castellanos Fernandez[18], Ajay K. Duseja[19], Jörn M. Schattenberg[20], Patrizia Burra[21], Maria Patrizia Carrieri[22], Marco Arrese[23], Mary Rinella[24], Ashwani K. Singal[25], Stuart C. Gordon[26], Michael Fuchs[27], Wayne Eskridge[28], Naim Alkhouri[29], Kenneth Cusi[30], Rohit Loomba[31,32], Jane Ranagan[33], Achim Kautz[34], Janus Ong[35], Marcelo Kugelmas[36], Yuichiro Eguchi[37], Moises Diago[38], Philip N. Newsome[39], Ming-Lung Yu[40], Lynn Gerber[1], Brian P. Lam[1], Lisa Fornaresio[41], Fatema Nader[42], Linda Henry[42], Andrei Racila[42], Pegah Golabi[1], Maria Stepanova[42] and Jeffrey V. Lazarus[43], (1)Inova Medicine, Inova Health System, Falls Church, VA, (2) Department of Gastroenterology, School of Medicine, Recep Tayip Erdogan University, Rize, Turkiye, (3) Department of Gastroenterology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, (4)Institute of Hepatology, Wenzhou Medical University, Wenzhou, China, (5)Department of Medicine, Liver Disease Research Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia, (6)Johns Hopkins University, (7)Endemic Medicine Department, Faculty of Medicine, Helwan University, Ain Helwan, Cairo, Egypt, (8)Department of Hepatology, Beaujon Hospital, AP-HP, Université Paris Cité, Inserm UMR1149, Clichy, France., (9)Department of Personality, Assessment, and Psychological Treatment, Faculty of Psychology, University of Seville, (10)Ucm Digestive Diseases, Virgen Del Rocio University Hospital, Instituto De Biomedicina De Sevilla, Ciberehd, University of Seville, Sevilla, Spain, (11)The Chinese University of Hong Kong, Hong Kong, China, (12) School of Public Health, University of Haifa, Haifa, Israel; Department of Gastroenterology, Tel-Aviv Medical Center, Tel-Aviv, Israel, (13)Chulalongkorn University, Bangkok, Thailand, (14)Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester MN, USA, (15)Liver Center, Saga University Hospital, (16)Kurume University School of Medicine, (17)Department of Gastroenterology and Hepatology, Antwerp University Hospital, Antwerp, Belgium, (18) Institute of Gastroenterology, University of Medical Sciences of Havana, Cuba, (19)Post Graduate Institute of Medical Education and Research, Chandigarh, India, (20)Metabolic Liver Research Program, I. Department of Medicine, University Medical Center Mainz, Mainz, Germany, (21)Gastroenterology, Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Via Giustiniani 2, Padua, Italy, (22)Aix Marseille Univ, Inserm, IRD, Sesstim, Sciences Economiques & Sociales De La Santé & Traitement De L'information Médicale, Marseille, France, (23)Departamento De Gastroenterologia, Escuela De Medicina, Pontificia Universidad Catolica De Chile, Santiago, Chile; Centro De Envejecimiento y Regeneración (CARE), Facultad De Ciencias Biológicas, Pontificia Universidad Católica De Chile, Santiago, Chile, (24)University of Chicago Pritzker School of Medicine; University of Chicago Hospitals, (25)Department of Medicine, University of South Dakota Sanford School of Medicine, Vermillion, SD, USA, (26)Division of Gastroenterology and Hepatology, Henry Ford Health, Detroit, MI, (27) Department of Medicine Mcguire Veterans' Affairs Medical Center, Richmond, Va; Department of Medicine Virginia Commonwealth University, Richmond, VA, USA, (28)Fatty Liver Foundation, Boise, ID, USA, (29) Arizona Liver Health, Phoenix, AZ, (30)Division of Endocrinology, Diabetes and Metabolism, University of Florida, Gainesville, FL, USA, (31)University of California, San Diego, San Diego, CA, (32)Division of Gastroenterology and Hepatology, Department of Medicine, NAFLD Research Center, University of California San Diego, La Jolla, CA, (33)Focus Medical Communications, (34)CEO of Kautz5 Gug, (35)College of Medicine, University of the Philippines, Manila, Philippines, (36)South Denver Gastroenterology, Englewood, Colorado, USA, (37)Liver Center, Saga University Hospital, Faculty of Medicine Saga University, Saga, Japan, (38)Departamento De Patología Digestiva, Consorcio Hospital General Universitario De Valencia, Valencia, Spain, (39)Centre for Liver and Gastrointestinal Research, Institute of Biomedical Research, Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham B15 2TT, UK, (40)Kaohsiung Chang Gung Memorial Hospital,, (41)Johns Hopkins University, Dept of

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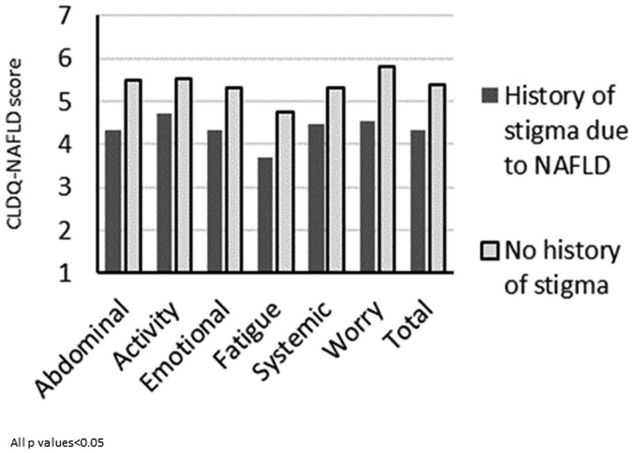
Background: Stigma can be associated with impairment of patients' quality-of-life. Aim: Evaluate the association between stigma and HRQL among NAFLD patients. **Methods:** NAFLD patients were invited to complete the Chronic Liver Disease Questionnaire-NAFLD (CLDQ-NASH; 36 items, 6 domains, range 1-7, higher scores = better HRQL) and a stigma survey about history of stigmatization or discrimination due to chronic conditions, various aspects of disease burden [Liver Disease Burden (LDB) instrument; 35 items, 7 domains including Stigma, range 1-4, higher scores = greater disease burden], and perception of various diagnostic terms. **Results:** The CLDQ-NASH and the stigma surveys were completed by 377 NAFLD patients (9% < 35 years, 52% male, 47% with ≥2 chronic comorbidities, 45% type 2 diabetes, 20% severe fibrosis or cirrhosis) from 12 countries (47% USA). Of included patients, 15% reported having experienced stigma or discrimination (at least sometimes) due to their liver disease (NAFLD) and 42% due to being overweight/obese. In addition, 26%, 35%, 23%, 25% reported feeling uncomfortable with the diagnostic terms "NAFLD", "fatty liver", "NASH" and "MAFLD", respectively. All aspects of NAFLD stigma (self-reported history of stigmatization due to the liver disease of NAFLD and having LDB Stigma score in top quartile) were associated with lower HRQL scores in all domains ($p \leq 0.01$) (Figure). In multivariate analysis adjusted for country of enrollment, history of stigmatization or discrimination due to the liver disease of NAFLD was the strongest independent predictor of lower HRQL scores in all domains (beta -0.63 to -0.92, $p < 0.001$) while history of stigmatization due to being overweight/obese was associated with lower Activity domain (beta = -0.36, $p = 0.01$). Negative perception of the diagnostic terms "NAFLD" or "NASH" was not associated with HRQL scores (all $p > 0.05$) while that of "fatty liver" or "MAFLD" was associated with impairment in Emotional, Fatigue, and Worry domains of CLDQ-NASH ($p < 0.01$). Other predictors of lower HRQL scores included female sex, lack of college education, having ≥2 chronic comorbidities, history of weight loss due to medical reasons, and having severe fibrosis or cirrhosis ($p < 0.05$). **Conclusion:** In this survey, 15% of NAFLD patients reported having experienced stigma or discrimination due to their liver disease and this was an independent predictor of impaired HRQL. Efforts should be made to better understand and reduce the sources of stigmatization or discrimination in patients with NAFLD.



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Laurent Castera – Echosens: Consultant, No, No; Madrigal: Consultant, No, No; MSD: Consultant, No, No; Novo Nordisk: Consultant, Yes, No; Pfizer: Consultant, No, No; Sagimet: Consultant, No, No; Echosens: Speaking and Teaching, No, No; Novo Nordisk: Speaking and Teaching, Yes, No;
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3813-C | SYMPTOM BURDEN, QUALITY OF LIFE, AND PALLIATIVE CARE IN END-STAGE LIVER DISEASE

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Background: End-Stage Liver Disease (ESLD) is a growing cause of mortality, suffering, and healthcare cost, all potentially modifiable by palliative care (PC) even with aggressive goals. PC is underutilized in ESLD, and actionable guidelines are lacking owing to lack of trial data. We conducted a pilot study of ESLD patients undergoing PC evaluation to guide future interventions. **Methods:** We enrolled patients admitted to our center for ESLD complications from 1/2022 to 11/2022. Demographic and clinical data were collected; surveys on symptom burden, quality of life (QOL), psychologic symptoms, and caregiver burden were conducted at baseline and at follow-up within 60 days; and readmission and mortality were collected. Every enrollee underwent PC evaluation regardless of care goals. Those readmitted within 60 days were compared to those who were not. **Results:** Twenty-eight patients were enrolled in the pilot. Mean age was 58 years, 61% were female, and 11% were Black. Etiology of liver disease was NASH in 36%, alcohol in 68%, and complications of portal hypertension, hepatic encephalopathy, ascites, and variceal bleed were present in 96%, 75%, 93%, and 21%, respectively with a median MELD-Na of 24.5. Median symptom burden measured by ESAS was moderate for pain (3.5), tiredness (5.5), and wellbeing (5). Median anxiety was mild by GAD 7 (7.5), and HADS Depression Score showed a median of 7.2. Mean QOL using the Short-Form Liver Disease QOL Survey was worst in Health Distress and Sleep domains (36.1 and 40.5, respectively), and highest in the Loneliness domain (82.3), with Symptoms, Effects, Concentration, Sexual functioning, Hopelessness, and Stigma domains ranging from 54.1 to 68.7). Mean caregiver burden by the Zarit Burden Interview was high (36.1). Mortality was 7%, and 47% were readmitted within 60 days of enrollment. Patients who were readmitted within 60 days had higher BMI, more burden in 7 out of 9 symptoms by ESAS, have more anxiety by GAD7, and have worse QOL in 7 out of 9 domains (Table 1). **Conclusion:** In a pilot study, symptom burden was high, quality of life was low, and readmitted patients appear to have more suffering and worse quality of life compared to patients who were not. This study supports the ability to offer PC to admitted patients in our institution and underscores its need from symptom burden, quality of life, and resource utilization perspectives. Next steps include creating and studying

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a comprehensive PC intervention in ESLD patients.

Table 1. Comparison between patients readmitted within 60 days and those who were not*

	Not re-admitted within 60 days, N = 10	Re-admitted within 60 days, N = 9	p
Age (mean, SD)	62.2 (13.0)	52.9 (12.6)	0.132
Gender (% Female)	60.0	55.6	1.000
Race % (Black/White/More than one race)	20.0/80.0/0	0/88.9/11.1	0.474
Advanced Care Plan Present (%)	50.0	22.2	0.350
Liver Disease Etiology NASH %	40.0	22.2	0.629
Liver Disease Etiology Alcohol %	60.0	77.8	0.629
Liver Disease Etiology HCV %	20.0	0	0.474
Liver Disease Etiology Other %	10.0	0	1.000
HE (%)	50	88.9	0.141
Ascites (%)	100	100	NA
Variceal Bleed (%)	50	11.1	0.141
MELDNa (Median, IQR)	24 (18,25)	24 (18,32)	0.288
CTP (Median, IQR)	10 (9,10)	10 (10,12)	0.245
BMI (Mean, SD)	24.5 (5.0)	33.4 (6.6)	0.018
Zarit (Mean, SD)	39.4 (16.6)	26 (7.1)	0.313
ESAS Average (Median, IQR)			
Pain	3 (0,6)	4 (0,5)	0.971
Tiredness	5 (3,8)	6 (5,9)	0.233
Nausea	0 (0,0)	2 (0,5)	0.043
Depression	0 (0,0)	3 (0,5)	0.048
Anxiety	0.5 (0,4)	3 (1,5)	0.300
Drowsiness	1 (0,5)	4 (2,5)	0.267
Appetite	3.5 (2,7)	3 (0,5)	0.353
Wellbeing	4 (1,5)	3 (3,6)	0.512
Shortness of Breath	1.5 (0,4)	6 (5,7)	0.058
GAD7 (Median, IQR)	5.5 (0,7)	12.5 (8,14.5)	0.013
SF-LDQOL Domains (mean, SD):			
Symptoms	58.1 (13.2)	52.6 (13.8)	0.385
Effects	71.7 (22.3)	47.2 (30.3)	0.060
Concentration	66.7 (33.2)	60.4 (30.3)	0.682
Health Distress	48.8 (35.6)	25.0 (34.7)	0.174
Sexual Functioning	66.0 (50.8)	58.2 (50.1)	0.943
Sleep	39.5 (23.3)	44.1 (18.7)	0.659
Loneliness	90.0 (16.3)	78.8 (23.6)	0.249
Hopelessness	67.6 (38.5)	84.4 (19.6)	0.285
Stigma	68.1 (36.5)	64.1 (26.7)	0.796
HADS Depression Score (Mean, SD)	6.5 (3.4)	7.4 (3.4)	0.575
HADS Anxiety Score (Mean, SD)	5.9 (5.0)	9.3 (4.6)	0.157

* To be eligible for this outcome (n=19), the enrollee must survive without discharge within 60 days of enrollment.
NASH (Non-Alcoholic Steatohepatitis); HCV (Hepatitis C Virus); HE (Hepatic Encephalopathy); MELDNa (Model of End-Stage Liver Disease Sodium); CTP (Child-Turcotte-Pugh); BMI (Body Mass Index); Zarit (Zarit Burden Interview for caregiver burden); ESAS (Edmonton Symptom Assessment System); GAD7 (General Anxiety Disorder-7); SF-LDQOL (Short Form - Liver Disease Quality of Life); HADS (Hospital Anxiety and Depression Scale)

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3814-C | TAILORED MESSAGE INTERVENTION BY NUDGE THEORY INCREASES THE NUMBER OF THE VIRAL HEPATITIS SCREENING FOR JAPANESE WORKERS AND CONSULTATION BEHAVIOR OF POSITIVE PATIENTS FOR HCV ANTIBODY- CONSIDERATION OF 1.8 MILLION GENERAL CHECK-UP PARTICIPANTS.

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Background: Although the overall number of hepatitis B virus (HBV) and hepatitis C virus (HCV) carriers in Japan has decreased, actions against hepatitis at work sites in Japan have not yet been fully implemented. In Japan Health Insurance Association (JHIA), which is belonged to more than 40 million Japanese who are working in Medium and Small Sized Companies, the number of hepatitis screening were less than 2 million from 2008 to 2016 even the cost of only $ 6. The aim of this study was to investigate the effectiveness of a tailored message intervention using nudge theory promoted the numbers of viral hepatitis screening and how many of those found to be positive for HCV antibody have been followed up with examinations and hospital treatment. **Methods:** About 1.8 million Japanese workers at Fukuoka branch of the JHIA who wish to get annual general checkup from 2017 to 2021 received client reminders by using nudge theory for an optional hepatitis virus screening. For control subjects, we enrolled general checkup applicants with typical message condition in 2016. The main outcome measure was attendance rates in HBV and HCV screening which were examined HBs antigen (HBsAg) and Anti-HCV antibody (HCVAb), respectively. In addition,12 months after the checkup, we analyzed how many workers who were positive for HCVAb visited to physicians by medical prescription system. **Results:** There was a significant difference in viral hepatitis screening attendance rates between the client reminders by using nudge theory ($n = 124,148$, 6.9%) and the control ($n = 4,791$, 1.2%; $p < 0.001$). One thousand one hundred thirty workers (0.91%) were positive of HBsAg ($n = 683$, 0.55%) and HCVAb ($n = 447$, 0.36%), respectively. The positive rate of HCV Ab in the 50s (0.59%) were higher than those in 60s (0.49%). Two hundred seventy-seven with HCVAb positive patients (61%) were confirmed to visit specialists 12 months after the screening. One hundred seventy (38%) were treated with IFN-free direct-acting antivirals and four males (0.8%) in 60s were detected hepatocellular carcinoma. **Conclusion:** There were still many positive patients with viral hepatitis at work sites. A simply modifying the client reminders using nudge theory could increase the viral hepatitis screening rates. Promoting hepatitis virus screening for workers at general checkup can rescue hepatitis virus carriers who are unaware of their infection and require to therapy for viral elimination and liver cancer.

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The following people have nothing to disclose: Masaaki Korenaga, Chieko Ohe, Keiko Kamimura, Keiko Korenaga, Tatsuya Ide

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

♦ 3922-C | SINGLE NUCLEUS RNA SEQUENCING UNVEILS A KEY IMMUNOLOGICAL PATHWAY INVOLVED IN LNCRNA H19-MEDIATED CHOLESTATIC LIVER INJURY

Xixian Jiang[1,2], Grayson Way[1], Jing Zeng[1], Derrick Zhao[1,2], Yun-Ling Tai[1], Lianyong Su[1,2], Xuan Wang[1], Phillip B. Hylemon[1,2] and Huiping Zhou[1,2], (1)Virginia Commonwealth University, (2)Richmond Veterans Affairs Medical Center

Background: Primary sclerosing cholangitis (PSC) remains a major clinical challenge due to the limited understanding of its pathogenesis and lack of effective treatments. Multidrug resistance 2 knockout (Mdr2$^{-/-}$) mouse is a well-accepted PSC model. Single-cell/nucleus transcriptomics has transformed the current understanding of the cell-type-specific role in liver disease. Our previous snRNA-seq studies reported that long non-coding RNA H19 (H19) is a critical regulator of cholestatic liver fibrosis, especially through regulating cholangiocyte differentiation, proliferation, and senescence. However, the cell type-specific role of H19 in modulating immune response in cholestatic liver disease remains unclear and is the focus of this study. **Methods:** C57/BL6 wild type (WT), Mdr2$^{-/-}$, H19$^{-/-}$ and Mdr2$^{-/-}$/H19$^{-/-}$ mice (female, 6-month-old) were used. The liver tissues were processed for snRNA-seq. Seurat package in R was used to analyze the snRNA-seq data. Cell-type-specific marker genes were used for the identification of cell types and the subsequent statistical analysis. QIAGEN Ingenuity Pathway Analysis (IPA) was used to identify both whole liver and cell-type-specific pathways regulated by H19 in Mdr2$^{-/-}$ mice. **Results:** All major hepatic cell types were successfully identified, including hepatocytes, cholangiocytes (CHO), hepatic stellate cells (HSCs), lymphocytes (Lyms), monocyte-derived macrophages (Md-MQs), Kupffer cells (KCs), myofibroblasts (MyoFs) and endothelial cells (ECs). The identification of cell types enabled us to compare the involvement of different cell types from different samples in chemokine signaling. As shown in Fig.1, Cxcl16 is markedly upregulated in Md-MQs and CHO of Mdr2$^{-/-}$ mice but downregulated in the Md-MQs and CHO of Mdr2$^{-/-}$/H19$^{-/-}$ mice. Cxcl16 is a chemokine that acts as a chemoattractant for the recruitment of various immune cells, including cytotoxic lymphocytes (CD8+ NKT cells and potentially NK&Th1 cells) through chemokine receptor Cxcr6. In Mdr2$^{-/-}$, Cxcr6 was significantly upregulated in Lyms, which was abrogated by the deletion of H19. **Conclusion:** Cxcl16 has diverse functions and has been implicated in various diseases by modulating immune cell migration and activation as well as the production of pro-inflammatory cytokines. Our study uncovered a cell-type-specific immunological pathway regulated by H19. These findings have the potential to identify new therapeutic targets or strategies for cholestatic liver injury.

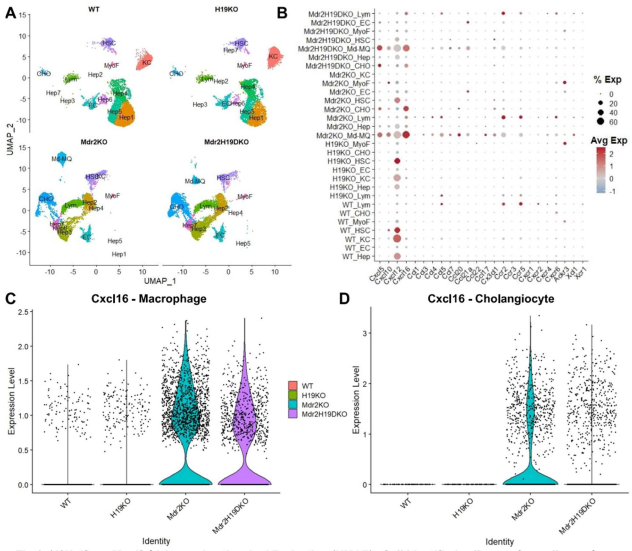

Fig 1. (A)Uniform Manifold Approximation And Projection (UMAP) of all identified cell types from all samples. (B)Dotplot of important chemokine signaling related genes in all cell types across all samples. (C)Violin plot of Cxcl16 expression in macrophage (KC & Md-MQ) populations cross all samples. (D)Violin plot of Cxcl16 expression in cholangiocyte populations cross all samples.

Disclosures: The following people have nothing to disclose: Xixian Jiang, Grayson Way, Jing Zeng, Derrick Zhao, Yun-Ling Tai, Lianyong Su, Xuan Wang, Phillip B. Hylemon, Huiping Zhou

3923-C | A STRUCTURAL AND MECHANISTIC MODEL FOR BSEP DYSFUNCTION IN SEVERE CHOLESTATIC DISEASE

Clemence Gruget[1], Bharat Reddy[2], Patrick Stoiber[2] and Jonathan Moore[1,2], (1)MIT, (2)Rectify Pharmaceuticals

Background: Bile salt efflux pump (BSEP, *ABCB11*) transports bile salts across the canalicular membrane of hepatocytes, for incorporation into bile. Biallelic mutations in BSEP can cause Progressive Familial Intrahepatic Cholestasis Type 2 (PFIC2), a pediatric disease characterized by hepatic bile acid accumulation leading to hepatotoxicity, and ultimately, liver failure. Missense variants comprise the preponderance of pathogenic genotypes but vary significantly in their degree of dysfunction, in a manner that predicts onset and severity of disease. Understanding the mechanism underlying the molecular dysfunction of disease-causing variants is important for the development of targeted pharmacotherapeutics that can rescue BSEP function as disease-modifying therapies for PFIC2. Here we undertake a biophysical characterization of 13 distinct PFIC2-associated variants. **Methods:** To characterize the effects of disease-causing mutations on protein

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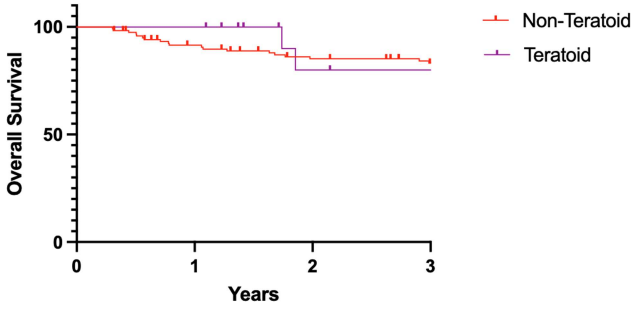
review demographics and outcomes of teratoid HB, a rare histological subtype, in a single tertiary referral center. **Methods:** A retrospective chart review showed a total of 136 treated HB patients from October 2004 to January 2022 at Texas Children's Hospital in Houston, Texas. Of the total cohort, 15 patients were found to have HB with teratoid histology. Teratoid histology was defined as HBs with epithelial and mesenchymal components with additional heterologous elements such as neuroepithelium, mucinous or squamous component, or melanin. **Results:** Teratoid HB was found to occur more often in males (73.3%) and Hispanic (60.0%) patients compared to those with other HB subtypes (64.4%, $p = 0.49$; 52.2%, $p = 0.50$). The median age at diagnosis of those with teratoid histology was 1.4 years (IQR 1.1-2.6) compared to 1.7 years (IQR 0.8-2.1, $p = 0.27$) in patients with non-teratoid histology. Patients with teratoid HB had a slightly higher incidence of prematurity at 46.6% compared to 35.5% in our entire cohort ($p = 0.39$). Pretreatment extent of disease (PRETEXT) IV was the most common diagnosis in teratoid (40.0%) and non-teratoid (33.6%) cohorts ($p = 0.62$). Metastatic disease was noted in 46.6% of teratoid patients compared to 22.3% of all non-teratoid patients ($p = 0.04$). Micro-vascular invasion was noted in 26.6% of patients with teratoid HB, while 60% had vascular invasion on pre-operative imaging compared to 34.5% ($p = 0.80$) and 56.6% ($p = 0.54$), respectively, in the non-teratoid cohort. 20% of both teratoid and non-teratoid cohorts had relapsed disease. Patients with teratoid HB had a 3-year overall survival (OS) of 82% compared to 87% in those without teratoid histology ($p = 0.92$). **Conclusion:** Teratoid HBs showed higher incidence of metastatic disease in our cohort. Despite this, patients with teratoid HB seem to have similar demographics, risk factors, and OS as non-teratoid HB. To our knowledge, this one of the largest series evaluating demographics and outcomes of teratoid HB.



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4081-A | INCREASING INCIDENCE OF LIVER CANCER IN OLD MEN: A POPULATION-BASED TIME-TREND ANALYSIS USING THE GLOBAL BURDEN OF DISEASES DATABASE, 1990-2019

Saqr Alsakarneh[1], Saeed Abughazaleh[2], Fouad Jaber[1], Remy Arwani[3], Mohammad Almeqdadi[4], Nikki Duong[5], Adel Muhanna[1], Kimberly Sanders[1], John Campbell[1], Anika Mittal[1] and Wendell K. Clarkston[1], (1)University of Missouri-Kansas City, (2)Tufts University, (3)Temple University, (4)Lahey Clinic Medical Center, (5)Virginia Commonwealth University Health System, Oakland, CA, United States

Background: Liver cancer is a leading cause of mortality in the US. Previous data showed an increasing incidence of liver cancer with greater rates in older adults. However, there are limited data on recent age and sex-specific incidence rates. The aim of this study was to conduct a time-trend analysis of liver cancer incidence rates using the Global Burden of Diseases (GBD) 2019 study database.
Methods: Data was obtained from the GBD 2019 database, an International database that covers 100% of liver cancer diagnosed cases in the US. Liver cancer incidence rates, age-adjusted to the standard US population, were calculated using SEER*Stat software (v.8.4.0.1, National Cancer Institute "NCI") and were stratified by gender, as reported in the database. Time-trends were estimated as annual percentage change (APC) and average APC (AAPC) using Joinpoint Regression Software (v.4.9.0.1, NCI) utilizing Monte Carlo permutation analysis to generate the simplest trend. Pairwise comparison was conducted between gender-specific trends using the tests of parallelism and coincidence. Age-specific trends were also assessed in two age sub-groups: younger adults aged 15-49 years and older adults aged 50-74 years. A two-sided P-value cut-off of 0.05 was utilized for statistical significance. **Results:** 483,002 patients were diagnosed with liver cancer in the US between 1990-2019. Overall, Liver cancer incidence rates have been significantly increasing in older adults but not in younger adults (AAPC = 3.32 vs 1.48; AAPC difference = 1.84, $P < 0.001$). Age-specific trends were not identical ($P < 0.001$) nor parallel ($P < 0.001$) suggesting that liver cancer incidence rates are different and increasing at a greater rate in older adults compared to younger adults. Similar results were seen in women (150,481 patients) with an absolute AAPC difference between older and younger adults of 0.46 ($P = 0.02$). However, in men (332,521 patients), while similar results were seen, a greater AAPC difference between younger and older men of 2.26 (< 0.001) was noted suggesting that the greatest disparity between liver cancer incidence trends between age-specific groups arises from men. **Conclusion:** Our results suggest that liver cancer

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incidence trends have been increasing in older adults while stable in younger adults over the last three decades. The greatest difference between older and younger adults seemed to be arising from older men. While this increase can be due to increase in morbidities commonly associated with aging like alcoholic liver disease and non-alcoholic fatty liver disease, it can also represent a true increase in incidence. Future studies are warranted to investigate risk factors associated with the increasing incidence in older adults, especially older men.

Trend analysis of Liver Cancer Age-Standardized Incidence rate with Gender and Age Variations from 1990 to 2019

Incidence	Trends[a]			Age and gender-specific AAPC difference (95% CI)	Pairwise comparison P-values		
	Time period	APC (95% CI)	AAPC (95% CI)		Age and gender-specific AAPC difference	Coincidence[b]	Parallelism[c]
All ages							
Young (15-49)	1990-2019	1.48 (0.78-2.18)	1.48 (0.78-2.18)	1.84 (2.52 to 1.15)	<0.001	<0.001	<0.001
Old (50-74)	1990-2019	3.32 (3.22-3.42)	3.32 (3.22-3.42)				
Males							
Young (15-49)	1990-2019	1.36 (0.56-2.17)	1.36 (0.56-2.17)	2.26 (3.04 to 1.48)	<0.001	<0.001	<0.001
Old (50-74)	1990-2019	3.62 (3.50-3.75)	3.62 (3.50-3.75)				
Females							
Young (15-49)	1990-2019	1.82 (1.40-2.24)	1.82 (1.40-2.24)	0.46 (0.87 to 0.04)	0.02	0.03	<0.001
Old (50-74)	1990-2019	2.28 (2.18-2.34)	2.28 (2.18-2.34)				

[a] Time-trends were computed using Joinpoint Regression Program (v4.9.0.1, NCI) with 2 maximum joinpoints allowed (3-line segments).
[b] Tests whether age/gender-specific trends were identical. A significant P-value indicates that the trends were not identical (i.e., they had different incidence rates and coincidence was rejected).
[c] Tests whether age/gender-specific trends were parallel. A significant P-value indicates that the trends were not parallel (i.e., parallelism was rejected).

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4082-A | INVASIVE MEASUREMENT OF HEPATIC VENOUS PORTAL GRADIENT BEFORE RESECTION OF HEPATOCELLULAR CARCINOMA

Petr Hříbek[1,2], Johana Klasová[1], Tomáš Tůma[1,2], Kateřina Menclová[1], Jiří Pudil[1] and Petr Urbánek[1], (1) Military University Hospital Prague, (2)University of Defense, Faculty of Military Health Sciences in Hradec Králové

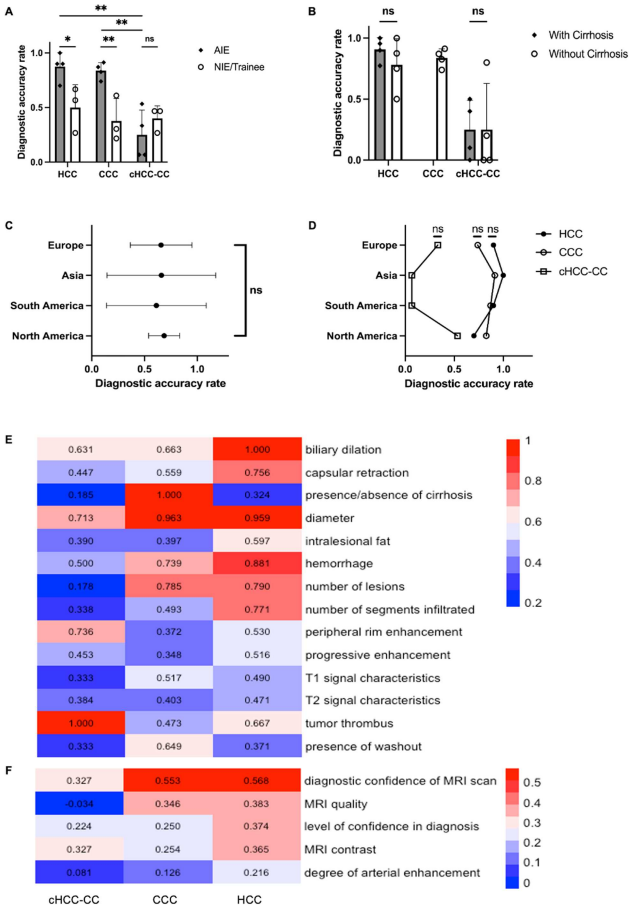
Background: Many patients with hepatocellular carcinoma (HCC) could not be transplanted for plenty of reasons. However, sugery remains option in terms of overall survival (OS). As most HCC develops in the field of liver cirrhosis, the presence of portal hypertension is crucial for liver resection (LR). Liver vein catheterization with hepatic venous-portal gradient (HVPG) measurement is the standard procedure for the quantification of portal hypertension. We prospectively followed a cohort of patients planned for LR with HVPG measurement before the decision on a definitive indication for surgery. **Methods:** We present: 1) a cohort of all patients who underwent HVPG measurement before planned LR for HCC between 1/2016–1/2023, 2) an analysis of complications of the procedure, and 3) overall outcomes. The cohort counted 35 patients with liver cirrhosis (30 males, mean age 69.5 y). In all patients upper endoscopy was realized to exclude esophageal rices before HVPG measurement. Patients included into our analysis were not suitable for liver transplantation according to current guidelines. **Results:** The success rate of HVPG measurement was 91.4%, with serious complications in 2.9% of cases. Due to clinically significant portal hypertension (CSPH), resection was contraindicated in 31.3% of patients. One patient (5.9%) had a complicated postoperative course with fasciitis. None of the other resected patients (88.2%) was rehospitalized for surgical complications or liver events until the 90th day after surgery, with no reported death. The median of overall survival (OS) in resected subgroup was 70 months (95% CI 52-86), and 35 months 95% (CI 13-48) in conservatively treated patients. **Conclusion:** HVPG measurement is the gold standard for the quantification of portal hypertension. Hepatic vein catheterization is invasive, but a safe procedure, with a clear impact on HCC management considered for surgery, especially with benefit for patients rejected from liver transplantation. In our cohort with HVPG-guided indication for resection, the liver event as a complication of surgery was identified only in 5.9% of cases.
Disclosures: The following people have nothing to disclose: Petr Hříbek, Johana Klasová, Tomáš Tůma, Kateřina Menclová, Jiří Pudil, Petr Urbánek

4083-A | INVESTIGATING HIGH RATES OF MISDIAGNOSIS AND POOR PROGNOSIS IN PRIMARY HEPATIC ANGIOSARCOMAS: A SYSTEMATIC REVIEW

Binyamin Ravina Abramowitz[1], Sanya Goswami[1] and Daniel Anthony DiLeo[2], (1)SUNY Downstate Health Sciences University, (2)VA New York Harbor Healthcare System

Background: Primary hepatic angiosarcoma (PHA) is a rare vascular malignancy of endothelial origin that accounts for only 2% of all hepatic primary tumors. It carries a poor prognosis given its highly malignant and rapidly progressive disease course. Its rarity has led to obscurity with its diverse clinical features making it an easily missed diagnosis for physicians. The diagnosis is confirmed via histopathology and a substantial percentage only by autopsy. We present a systematic review identifying patient cases of PHA to summarize and highlight new and existing literature to provide clarity of the challenges faced in the diagnosis and treatment of PHA. **Methods:** We performed a systematic literature search using predefined keywords within 3 databases (PubMed, EMBASE, and MEDLINE) to identify case reports and case series of PHA within the past ten years. A set exclusion criteria was applied. All remaining articles were assessed for selection and subsequent data extraction. We analyzed pooled individual clinical data regarding demographics, symptoms, treatments, and prognosis. **Results:** A total of 65 patients from 59 case

Results: The AIEs exhibited high proficiency in utilizing MRI images exclusively for the diagnosis of HCC (70%-100%) and CCC (73.9%-91.3%). They outperformed NIEs/trainees (all p values < 0.01), achieving correct rates of 26.7%-66.7% for HCC and 21.7%-60.9% for CCC. However, their ability to accurately distinguish cHCC-CC (6.7%-53.3%) was limited and comparable to NIEs/trainees (26.7%-46.7%). Furthermore, there was greater consistency in MRI feature assessment among AIEs for HCC and CCC when compared to cHCC-CC. Notably, there were no significant differences observed in the impact of a cirrhotic background on the diagnosis of HCC and cHCC-CC among AIEs. Moreover, there was non-significant inter-continental variability in overall liver cancer diagnosis and the diagnosis rates of the three types of liver cancer by AIEs. **Conclusion:** MRI imaging showed good discrimination between HCC and CCC particularly when diagnosed by abdominal imaging experts. However, accuracy in detecting cHCC-CC was very limited among all participating radiologists. Thus, liver biopsy remains important for the accuracy of diagnosis and selection of medical treatment modalities.



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4160-A | CLINICAL PHENOTYPES OF BENIGN HEPATIC LESIONS

Michael Bradley Andrews[1], Manaswitha Thota[1], Jonathan Paul Van Name[1], Tamas Gal[1] and Richard K. Sterling[2], (1)Virginia Commonwealth University, (2) Virginia Commonwealth University Health System

Background: Most benign hepatic lesions occur in isolation. The clinical and demographic phenotype in patients (pts) with more than one lesion can overlap making treatment decisions challenging. To address this gap in knowledge, our aim was to describe the clinical and demographic characteristics in a cohort of pts with benign hepatic lesions to predict the lesion based on clinical data and oral contraceptive (OCP) use. We particularly wanted to know how common the two more clinically relevant lesions, hepatic adenoma (HA) and focal nodular hyperplasia (FNH) occurred and could a "clinical phenotype" identify these patients. **Methods:** This was a single institution retrospective case series using bioinformatics and natural language processing to identify eligible pts with HA, FNH, hemangioma (HM), and cysts (C) undergoing imaging (MRI, CT, or US). Demographics and laboratory values such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, hemoglobin (Hgb), platelets, prothrombin time (PT), and OCP use were collected. Descriptive analysis was performed. Differences between groups were assessed by ANOVA or Wilcoxon tests for continuous variables and chi-square for categorical variables with alpha 0.05. Variables identified on univariate analysis with $p < 0.2$ were included in multivariate analysis to identify independent factors associated with the different lesion groups. **Results:** The statistically significant differences across all groups ($n = 216$) on univariate ANOVA were age, sex, AST, ALP, albumin, Hgb, platelets, PT, and OCP use (Table). After adjusting for ALT in the multivariate model, statistically significant differences across all groups were age, sex, ALP, and Hgb. The statistically significant differences between HA and FNH on univariate ANOVA were sex, AST, ALT, ALP, albumin, and Hgb. After adjusting for platelets, PT and OCP use, there remained significant differences in ALP and Hgb between those with HA and those with FNH. Combination lesions were observed in 28 (12%): C + HM (2), C + FNH (8), C + HA (4), HM + FNH (7), HA + HM (2), FHN + HM (1), and HA + FNH (4). **Conclusion:** Predicting the etiology of benign hepatic lesions based on patient demographics, common

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laboratory values, and a brief history including OCP use alone is difficult. However, we identified the most important demographic (age, sex) and laboratory values (ALP, Hgb) to assist in building a differential.

Table. Comparison of lesions

Characteristic	FNH	HA	Cyst	Hemangioma	FNH+ HA	Univariate / multivariate p-values
N	90	47	60	16	3	
Age (years)^	37.68(11.9)	38.0 (13.5)	62.1 (13.9)	48.6 (12.6)	41 (19.5)	<.0001/<.001
Sex (% Female)	81	95	50	31	100	<.0001/.0013
Race (% White)	47	62	58	69	67	.37
Ethnicity (%Non-Hispanic)	94	94	95	100	100	.74
AST U/L ^^	30 (31)	48.9 (76)	34 (33)	45 (40)	23 (11.7)	.047
ALT U/L ^^	29 (30)	64 (144)	27 (29)	41 (33)	26 (9.5)	.09 .01 HA vs cyst and HA vs FNH
ALP U/L ^^	90 (35)	123(111)	87 (31)	130 (83)	100 (20)	.015/.0156
Bilirubin mg/dl ^^	0.57 (.56)	0.49 (.25)	0.70 (.38)	0.45 (.20)	0.33 (.15)	.12
Albumin g/L ^	4.3 (.36)	4.17 (.41)	4.00 (.63)	3.96 (.68)	3.9 (.68)	.003
WBC ^^	7.7 (2.54)	8.3 (3.94)	7.6 (2.65)	8.16 (3.9)	8.3 (0.9)	.75
Hgb ^	13.2 (1.5)	12.1 (1.5)	12.7 (2.2)	12.3 (2.4)	11.7 (2.8)	.027/.02
Hct ^ (n=110)						
Platelet (x 1000) ^^	287 (79)	311 (124)	241 (131)	276 (140)	345 (23)	.0148
FIB-4	.86 (.85)	.86 (.63)	5.1 (21)	1.8 (1.5)	.52 (.17)	.24
PT (sec) ^	13.1 (2.2)	12.6 (2.3)	14.5 (2.7)	13.9 (1.6)	10.9 (1.7)	.006
INR ^ (n= 189)	1.05 (.15)	1.05 (.11)	1.14 (.27)	1.1 (.14)	1 (0)	.047
Cr	0.93 (1.4)	0.72 (.16)	1.07 (1.1)	1.25 (1.03)	0.62 (.007)	.44
HCV Ab +	2%	0%	16%	66%	0%	<.0001
Contraceptive use	35	53	2%	12	33	<.0001
Imaging modality	MRI 85% CT 14% US 1%	MRI 78% CT 19% US 2%	MRI 20% CT 72% US 8%	MRI 39% CT 39% US 22%	MRI 100%	<.0001
Number of lesions	1: 54% 2: 20% 3: 11% >=4: 11%	1: 51% 2: 4% 3: 6% >=4: 38%				
Largest Size	4.7 cm 95% CI 2.17-2.29	4.92 (95% CI 2.99-4.52)		3.1 cm 95% CI 2.17-2.93		
Single lesion	44%	42%	100%	87%	0	<.001

^ mean (SD) ^^ Median (IQR)

Disclosures: The following people have nothing to disclose: Michael Bradley Andrews, Manaswitha Thota, Jonathan Paul Van Name, Tamas Gal, Richard K. Sterling

4161-A | CLINICOPATHOLOGICAL CHARACTERISTICS AND MOLECULAR ANALYSIS OF LYMPHOCYTE-RICH HCC

Kana Tsutsui[1], Masamichi Nakayama[1], Sachiko Ogasawara[1], Jun Akiba[2] and Hirohisa Yano[1], (1) Kurume University School of Medicine, (2)Kurume University Hospital

Background: In the WHO Classification of Digestive System Tumours, 5th Edition (2019), a new subtype of hepatocellular carcinoma (HCC), designated lymphocyte-rich HCC (LR-HCC), has been proposed. In LR-HCC, lymphocytes outnumber tumor cells in most fields on H&E staining. HCC is one of the malignant tumors with poor prognosis, whereas this new subtype is considered to have a relatively good prognosis. As it is a newly proposed subtype with rare frequency (< 1% of all HCCs), there have been few coherent reports on its clinical and pathological features. In this study, we examined the clinicopathological and molecular features of LR-HCC. **Methods:** 1) In the present study, 451 surgically-resected HCC cases without previous treatment history from 2012 to 2021 at our hospital were analyzed. Clinicopathological characteristics of LR-HCC and the other HCC (non-LR-HCC) subtypes were compared. To evaluate intratumoral infiltrating lymphocytes, immunostaining for CD3, CD20, and CD8 was performed in LR-HCC. 2) Neoplastic and nonneoplastic hepatocytes from LR-HCC (n = 4) were collected with a laser microdissection system, and RNA was extracted, followed by microarray analysis to examine molecules involved in lymphocytic infiltration. 3) The immunohistochemical expression of identified molecules was examined in LR-HCC (28 cases) and non-LR-HCC (30 cases). **Results:** 1) There were 28 cases (6%) of LR-HCC. No statistically significant differences were found in the clinicopathological features, including prognosis, between LR-HCC and non-LR-HCC cases. The 5-year survival rate for LR-HCC was over 90%. There were significantly more CD3+ cells than CD20+ cells ($p < 0.0001$) in tumor infiltrating lymphocytes, and most of them were CD8+ T cells. 2) Microarray analysis revealed that CCL20 which induces lymphocyte migration, was highly expressed in LR-HCC cases. 3) Immunohistochemical study revealed that CCL20 expression was significantly higher in LR-HCC ($p < 0.01$) tumor cells compared with non-LR-HCC. Expression of CCR6, the only known receptor for CCL20, was confirmed in infiltrating lymphocytes in LR-HCC. **Conclusion:** This study suggests that LR-HCC is not a very rare subtype with no significant differences in clinicopathological features compared with non-LR-HCC subtypes although the 5-year survival rate was favorable and over 90%. CCL20 expression appears to contribute to rich CD8+ lymphocyte infiltration in LR-HCC.

Disclosures: The following people have nothing to disclose: Kana Tsutsui, Masamichi Nakayama, Sachiko Ogasawara, Jun Akiba, Hirohisa Yano

4162-A | CONTRAST-ENHANCED ULTRASOUND (CEUS) FOR THE DIAGNOSIS OF HEPATOCELLULAR CARCINOMA (HCC) IN ADULTS WITH CHRONIC LIVER DISEASE. A COCHRANE SYSTEMATIC REVIEW AND METANALYSIS

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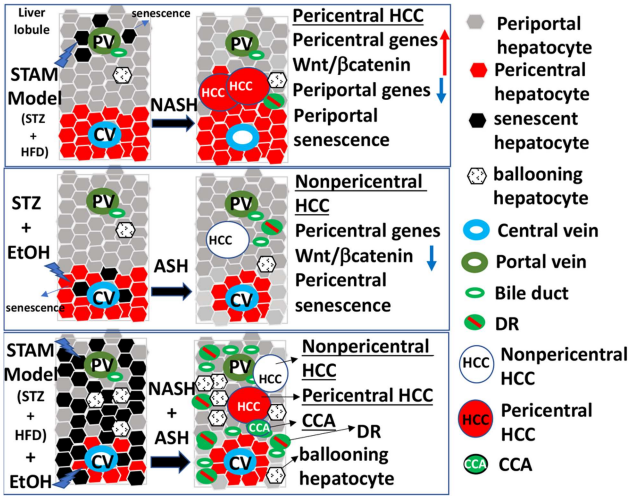
cell death using barcoded antibodies. **Results:** Pericentralized/deperiportalized tumors expressing gene signatures like Hoshida subclass S3 in human HCC that contained ß-catenin mutations were found in the STAM model. These tumors resulted from periportal senescence and upregulated Wnt/ß-catenin targets including glutamine synthetase (Gs), and downregulation of genes in urea cycle, amino acid catabolism, and growth hormone/Ras signaling. Superimposed alcohol exposure in the STAM model exacerbated steatosis, hepatocyte damage, and ductular reaction (DR). Although alcohol decreased occurrence rates of the Gs^+ HCC, it provoked nonpericentral Gs^- tumors and promoted cytokeratin 19^+ cholangiocarcinoma (CCA). In the third model, alcohol alone after STZ administration caused pericentral senescence and triggered HCC that was opposite to the Gs^+ NASH-HCC in the STAM model. We observed downregulation of Wnt/ß-catenin targets including stemness regulators Lgr5, Tbx3, axin2, and Lef1. This type of ASH-HCC resembled Hoshida subclass S1 of human HCC with predominant activation of transforming growth factor (TGF)ß and Myc pathways. Furthermore, the ASH-HCC were Gs^- depericentral tumors and mimicked metabolic reprogramming in human livers with alcoholic hepatitis (AH). DSP revealed differential immune cell infiltrations and cell death activation in cell fractions of Gs^+ HCC, Gs-HCC, and CCA compared to intratumoral myofibroblasts, and their adjacent tissues. **Conclusion:** HFD induces Gs^+ pericentral HCC due to periportal senescence in the STAM model, whereas alcohol inhibits the Gs^- depericentral HCC. Superimposed alcohol exposure causes synergistic effects of NASH and ASH that exacerbates steatosis, hepatocyte damage, and DR leading to tumor heterogeneity with extensive DR and mixed HCC/CCA. These models mimic liver pathologies in human HCC/CCA and provide new platforms to dissect molecular mechanisms of distinct hepatocarcinogenesis among NASH, ASH, or both.



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4300-A | 25HC3S ALLEVIATES INJURED LIVER FUNCTION AND DECREASES MORTALITY BY PROMOTER 5mCpG DEMETHYLATION SIGNALING PATHWAYS

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Background: Acute liver failure (ALF) is a dramatic and devastating disease. ALF often results in severe hepatocyte injury and apoptosis, leading to massive necrosis in the liver and the sudden death. Severe lipopolysaccharide (LPS)- and acetaminophen (ATMP)-induced hepatotoxicity are the most frequent causes of ALF. Currently, treatment options for ALF are extremely limited. 25-Hydroxycholesterol 3-sulfate (25HC3S, DUR928, or larsucosterol) has been demonstrated to alleviate injured liver function and decrease mortality in the acute liver failure in mouse models. The present study was designed to explore molecular mechanism(s) by which 25HC3S can be used to treat ALF. **Methods:** ALF mouse models were established by intravenous injection with LPS or ATMP. The injured liver function was treated with intraperitoneal administration of 25HC3S. Serum enzymatic activities were determined in our clinic laboratory. Western blot and mRNA sequencings were used to determine levels of gene expression; Whole genome bisulfite sequencing (WGBS) analysis was used to determine demethylation of ^{5m}CpG in promoter regions; DSS software (DSS 2.34.0) was used to identify differentially methylated regions (DMRs); and KOBAS software (KOBAS 2.0) was to test the statistical enrichment of DMR related genes in KEGG pathways. **Results:** Administration of 25HC3S decreased serum liver-impaired markers and alleviated liver, lung, and kidney injury. Subsequently, 25HC3S increased the survival rates in the LPS- or ATMP-induced mouse model, only 10% of the animals survived 96 hours without 25HC3S versus 90% survival with the 25HC3S. These effects resulted from the inhibition of the expression of genes involved in the pro-inflammatory response and apoptosis as well as the simultaneous induction of the expression of genes involved in cell survival. WGBS analysis showed that 25HC3S increased demethylation of ^{5m}CpG in key promoter regions and thereby increased expression of

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genes involved in the MAPK-ERK and PI3K-Akt signaling pathways. 25HC3S exhibited significantly stronger effects in these activities, indicating that 25HC3S, a potent epigenetic regulator, plays an important role in the inflammatory response, cell apoptosis, and cell survival by demethylation of promoter ^{5m}CpG and upregulation of MAPK and PI3K signaling pathways in vivo. **Conclusion:** 25HC3S is a potent epigenetic regulator and has the potential to serve as a novel biomedicine in the therapy of ALF and acute multiple organ failure.

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◆ 4301-A | A SIMPLE DYNAMIC SCORE ILBS-ALF-DYNAMIC SCORE (ILADS) RELIABLY PREDICTS MORTALITY IN ACUTE LIVER FAILURE PATIENTS WITH CEREBRAL EDEMA

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Background: The outcomes of acute liver failure (ALF) have improved with increasing use of therapeutic plasma-exchange (TPE) and continuous renal replacement therapy (CRRT). Currently, there are no dynamic scores which incorporate assessment of cerebral edema, and impact of these therapeutic modalities for determining outcome in these patients. **Methods:** Prospective cohort of 170 adult patients with ALF requiring mechanical ventilation for cerebral edema (confirmed by CT-scan) with no option of liver transplant were enrolled. One point each for the class value was assigned for the significant parameters from the Cox-regression model for the calculation of the score for prediction of 21-day mortality. The score was calculated for day 2 and day 3 and compared to the other prognostic scores. **Results:** Patients with ALF (aged 31.0 ± 11.0 yrs, 47.6% males, 33% meeting KCH criteria 79% viral-related, 50% with sepsis) were enrolled of which 47.6% died. Sixty-one patients (36%) underwent TPE and/or CRRT. Five dynamic variables serum bilirubin (mg/dl) [(< 12 vs 12-18 vs. ≥ 18) [HR 1:2.11(1.10,4.04):3.59(1.99,6.46)], arterial lactate;(umol/L)[< 2.6 vs.2.6-5.0 vs. ≥ 5) [HR1:(3.84,1.72-8.57):(6.66,2.95-15.04)], ammonia ≥ 211mg/dl, (HR 1.90 (1.19-3.02) international normalized ratio (INR) ≥ 4.16 (HR 2.78,1.79-4.30) and optic nerve sheath diameter (ONSD) (< 4.5 vs.4.5-5.12 vs. ≥ 5.12 mm) [HR 1: (2.82,1.34-5.93): (5.32,2.58-10.96) and 2 fixed variables jaundice-to-encephalopathy time (days) (HR1.05 ,1.01-1.09) and age (≥ 32 y) (HR 2.13, (1.38-3.30) predicted 21-day mortality. With each unit increase in the (ILADS) ILbs-ALF-Dynamic Score, the hazard of death increased by 49% [HR1.4, 1.3-1.6)]. Patients who underwent TPE/CRRT had significantly lower mortality (26.4% vs 57.3%; $p < 0.001$, HR 0.43, 0.24-0.78). The ILADS ≥ 12 at day 1 (sensitivity 95.5%, specificity 72.0%; AUROC 0.89 (0.79-0.94)] and ILADS ≥ 11 at day 2 or 3 for patients who underwent TPE/CRRT (sensitivity 92.3%, specificity 53.8%; AUROC 0.80 (0.67-0.92)] accurately predicted mortality. At day 2, a progressive or persistent increase in serum bilirubin (≥ 16mg/dl); (HR 2.381.53,3.70), lactate (≥ 3.9 umol/L) (HR 2.85,1.76,4.59), ammonia (≥ 410 mg/dl) (HR 1.65, 0.82-3.30), INR (≥ 6.7) (HR 3.22,1.88,5.51) and ONSD (≥ 4.0mm)(HR 2.49,1.59,3.89) independently predicted worse outcomes. The ILADS score performed better than other scores; Harrell's C-index; ILADS (0.78), SOFA (0.61), APACHE (0.60), ALFED (0.62) and KCH (0.61). **Conclusion:** The ILADS score comprising of 5 simple dynamic and 2 fixed prognostic variables can reliably stratify patients of ALF with cerebral edema at high risk of 21-day mortality. Therapeutic interventions targeting the components of ILADS could be assessed dynamically with the score to stratify patients for super-urgent liver transplant.

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◆ 4302-A | ACTIVATION OF HEPATOCYTE p53 TRIGGERS ACUTE LIVER FAILURE WITH MULTIPLE ORGAN DYSFUNCTION.

Jihyun Sung[1], Hayato Hikita[1], Yuki Makino[1], Seiya Kato[1], Yoichi Sasaki[1], Kenji Fukumoto[1], Kazuhiro Murai[1], Kunimaro Furuta[1], Akira Nishio[1], Takahiro Kodama[2], Tomohide Tatsumi[1] and Tetsuo Takehara[2], (1)Osaka University, Graduate School of Medicine, (2) Osaka University Graduate School of Medicine

Background: Acute liver failure (ALF) is characterized by massive hepatocyte cell death in a short term for which no effective treatment exists except liver

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

Conclusion: Considering there are no treatments available to alleviate or reverse the disease state in the progression of ALD, explicitly understanding the specific molecular mechanisms that contribute to observed clinical pathologies is essential in identifying novel therapeutic targets. Since peroxisomes are involved in a wide array of cellular functions including, but not restricted to, regulating oxidative stress and lipid homeostasis, investigating their response to alcohol is of paramount importance.
Disclosures: The following people have nothing to disclose: Ramyajit Mitra, Oluwaseyi Okesooto
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4417-A | CHOLESTENOIC ACID AS ENDOGENOUS EPIGENETIC REGULATOR DECREASES LIPID ACCUMULATION IN HUMAN HEPATOCYTES

Yaping Wang, William Pandak and Shunlin Ren, Virginia Commonwealth University

Background: Cholestenoic acid (CA), along with 27HC and 25HC, is a natural ligand for LXRs and is synthesized in mitochondria. Previous studies have demonstrated the involvement of 27HC and 25HC in lipid metabolism, inflammatory responses, and cell apoptosis. However, the physiological and pathological roles of CA remain unclear. This study aimed to investigate the molecular mechanism underlying the potential role of CA in hepatic lipid homeostasis. **Methods:** Enzyme kinetic analysis was utilized to examine the impact of CA on the activities of three DNA methyltransferases (DNMTs). Human hepatocytes cultured in high glucose medium were utilized as a non-alcoholic fatty liver disease model. Human whole-genome bisulfite sequencing (WGBS) and messenger RNA sequencing were used to investigate the relationship between DNA methylation and gene expression. Additionally, untargeted lipidomics analysis was performed to assess the impact of CA on lipid levels. **Results:** Enzyme kinetic studies revealed that CA specifically inhibits the activity of DNMTs.WGBS analysis showed an increased number of differential methylation regions (DMRs) over time between the control and CA-treated groups. Hypomethylated DMRs in the promoter region after CA treatment were significantly enriched in lipid metabolism-related processes and metabolic signaling pathways. mRNA sequencing analysis indicated significant modulation of numerous gene clusters by CA, with the number of differentially expressed genes increasing over time. Down-regulated genes were significantly enriched in lipid biosynthesis processes and KEGG pathways related to steroid biosynthesis, terpenoid backbone biosynthesis, metabolic pathways, and cholesterol metabolism. RT-qPCR and western blot analyses validated the results of RNA sequencing and WGBS, confirming the time- and dose-dependent decrease in gene expression and protein levels of key genes involved in lipid synthesis, along with the increase in regulatory genes associated with calcium and ERK signaling pathways. Untargeted lipidomics analysis further demonstrated that CA significantly decreased lipid levels. **Conclusion:** This study highlights CA as a distinct endogenous epigenetic regulator that decreases lipid accumulation in human hepatocytes by demethylating DNA ^{5m}CpG of essential genes involved in hepatic lipid metabolism. This study emphasize the significance of CA as a potential therapeutic target for metabolic disorders, specifically hyperlipidemias.
Disclosures: Shunlin Ren – License related payment from DURECT Co.: Royalties or patent beneficiary, No, No;
The following people have nothing to disclose: Yaping Wang, William Pandak

4418-A | DISCOVERY OF A NOVEL REGULATORY MOLECULE: 3β-HYDROXY-5-CHOLESTENOIC ACID 3-SULFATE, SECRETED BY HEPATOCYTES AND SUPPRESSES INFLAMMATORY RESPONSES IN MACROPHAGES

Yaping Wang, William Pandak and Shunlin Ren, Virginia Commonwealth University

Background: Cholestenoic acid (CA) is a natural ligand for LXRs and is synthesized in mitochondria, along with 27HC and 25HC. Our previous study uncovered CA as an endogenous epigenetic regulator that reduces lipid accumulation in human hepatocytes by demethylating key genes related to lipid metabolism. Nevertheless, the metabolic pathway of CA remains elusive. This study aims to investigate the metabolic pathway of CA in human hepatocytes and explore the biological functions of its metabolites. **Methods:** LC-MS/MS was used to monitor the metabolic pathway of CA in human hepatocytes. Human hepatocytes cultured in high glucose medium were used as a non-alcoholic fatty liver disease (NAFLD) model to examine the effect of CA3S on lipid metabolism. Human macrophage cells induced by 2 ug/ml Lipopolysaccharide (LPS) were used as an inflammation response model to investigate the effect of CA3S on inflammation response. RT-qPCR was used to analyze the effect of CA3S on gene expression related to lipid metabolism and inflammation response. **Results:** HepG-2 cells were treated with 20 uM CA for various durations (0, 1.5, 3, 6, 12, and

24 hours). The cultured media samples were collected, extracted, and analyzed using LC-MS/MS. The results showed a decrease in CA (m/z 415) levels in the cultured media as culturing time increased. A new molecular ion (m/z) 495 appeared at 1.5 hours and reached a maximum (90%) at 24 hours. Further investigation using tandem MS fragmentation revealed three major fragments: m/z 80, m/z 97, and m/z 415. Comparison with a synthesized compound confirmed the new m/z 495 compound as 3β-hydroxy-5-cholestenoic acid 3-sulfate (CA3S). The analysis revealed the presence of CA3S in the intercellular space of HepG-2 cells with CA treatment, indicating its sulfation and release from hepatocytes. To explore its biological function, CA3S was synthesized and purified in the lab. Treatment of HepG-2 cells with purified CA3S down-regulated lipid biosynthesis genes (hmgr, fas, and pcsk9) according to RT-qPCR results. Additionally, treating macrophage cells with CA3S significantly reduced the expression of inflammatory cytokine genes (il-1a, il-6, and cox2) induced by LPS, as demonstrated by RT-qPCR. **Conclusion:** Our findings indicate that CA can be sulfated to CA3S in human hepatocytes and subsequently released. CA3S exhibits an anti-inflammatory effect on human macrophage cells, suggesting its potential as a therapeutic agent for inflammation-related conditions.

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4419-A | EFFICACY OF VEGFR2-TARGETED THERAPY AFTER ATEZOLIZUMAB AND BEVACIZUMAB COMBINATION THERAPY IN HEPATOCELLULAR CARCINOMA

Kouki Nio[1], Gen Sugiyama[1], Hikari Okada[1] and Taro Yamashita[2], (1)Kanazawa University Graduate School of Medicine, (2)Kanazawa University

Background: Atezolizumab, an anti-PD-L1 antibody, plus bevacizumab, an anti-VEGFA antibody, combination (ABC) therapy for advanced hepatocellular carcinoma (HCC) has widely been used in clinical practice as a first-line treatment. Ramucirumab, an anti-VEGFR2 antibody, has been shown to be effective for advanced HCC with high AFP levels, but its efficacy after ABC therapy is unclear. In this study, we aimed to analyze the effect of the anti-VEGFR2 antibody after combination therapy with anti-PD-L1 and anti-VEGFA antibodies in vivo. **Methods:** A patient-derived xenograft (PDX) model was used to confirm the efficacy of anti-mouse VEGFR2 antibody (DC101), provided by Eli Lilly and Company, on human HCC xenograft. A syngeneic mouse model of AFP/EpCAM-positive HCC, which shows poor prognosis with stem cell features, was used to assess the efficacy of DC101 after combination therapy with anti-PD-L1 and anti-VEGFA antibodies. The dose of 40 mg/kg/mouse of DC101 was administered intraperitoneally to mice twice a week. In a syngeneic model, DC101 was administered for 5 weeks sequentially after 2 weeks of combination therapy. Gene expression in tumor tissues was examined by microarray expression analysis. Protein expression in tumor tissues was determined by immunohistochemical staining, immunofluorescent staining, and multiplexed spatial proteomics. The identity of single cells in tumor tissue was defined by protein expression profiles from multiplex spatial proteomics **Results:** In a PDX model, DC101 significantly suppressed tumor growth with the inhibition of the proximity of AFP-positive human HCC cells and VEGFR2-positive mouse vascular endothelial cells. In addition, in a syngeneic mouse model, sequential DC101 treatment after combination therapy showed a significant anti-tumor effect. Analysis of gene and protein expression in tumor tissues revealed that DC101 significantly suppressed a stem cell marker EpCAM expression as well as the vascular endothelial marker. Interestingly, DC101 treatment reduced the number of CD8-T cells positive for PD-L1 and TIGIT in tumor tissues, which are immune checkpoint molecules associated with T-cell exhaustion. **Conclusion:** The anti-VEGFR2 antibody not only inhibits angiogenesis but also suppresses cancer stem cells and activates tumor immunity, and it might be effective in AFP-positive advanced HCC after ABC therapy.

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Disclosure information not available at the time of publication: Gen Sugiyama, Hikari Okada

4420-A | EFFICIENT ENGRAFTMENT, VIRAL TRANSDUCTION AND CORRECTION OF LIPID ACCUMULATION IN HUMAN HEPATOCYTES IN AN FRG RAT LIVER HUMANIZATION MODEL

Marisa Carbonaro and Zhe Li, Regeneron Pharmaceuticals

Background: Humanized liver models, in which the host liver parenchyma is replaced by human hepatocytes, have been increasingly used in drug development and disease research. In the leading humanized liver mouse model, Fumarylacetoacetate Hydrolase (Fah), Recombination Activating Gene (Rag)-2 and Interleukin-2 Receptor Gamma (Il2rg) genes are

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